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METHIMAZOLE AND CARBIMAZOLE IN HYPERTHYROIDISM: A COMPARISON BY A DOUBLE BLIND TECHNIQUE

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In 1949, Stanley and Astwood called attention to the hitherto overlooked highly suppressive influence of certain imidazoles on the uptake of iodine by the human thyroid gland[21]. They were particularly impressed with the usefulness of methimazole (1-methyl-2-mercaptoimidazole) in suppressing radio-iodine uptake and controlling the manifestations of thyrotoxicosis[21]. More recently Lawson, Rimington and Searle have suggested that the imidazole action could be prolonged by the substitution of a carbethoxy group for the hydrogen of the mercapto group on carbon atom two of methimazole[13]. In clinical trial, this compound, carbimazole, has proven about as effective, weight for weight, as methimazole in the management of thyrotoxicosis (Bartels[2], Beierwaltes[3], Chevalley *et al.*[4], Crooks[5], Doniach[6,7], Fraser *et al.*[8], Harrison[9], Henderson[10], Kirkeby and Romeke[11], Lawson and Barry[12], Lawson, Rimington and Searle[13], MacGregor and Miller[14], McGavack *et al.*[15], Poate[16], Reveno and Rosenbaum[17], Richardson, Sarkany and Campbell[18]).

It has been somewhat more difficult to decide which of the two imidazoles, methimazole or carbimazole, is the more toxic. It has been claimed that methimazole is too toxic for other than preoperative care (Stone, Petit and Starr[23]) while other investigators, in earlier reports, recorded no instances of toxic effects (Beierwaltes[3], Reveno and Rosenbaum[17], Stone *et al.*[22]). The administration of carbimazole has been attended by remarkably few side effects in the hands of most workers (Ayad[1], Bartels[2], Chevalley *et al.*[4], Crooks[5], Doniach[6,7], Fraser *et al.*[8], Harrison[9], Henderson[10], Kirkeby and Romeke[11], Lawson and Barry[12], Lawson, Rimington and Searle[13], McGavack *et al.*[15], Poate[16], Richardson, Sarkany and Campbell[18], Soberon and Rodriquez[19], Staffieri and Cardonnet[20]). However, Bartels recorded side effects in 5.8% of 52 patients[2]. In an analysis of more than 500 cases from the literature, including Bartels' patients just mentioned, we arrived at an overall incidence of 1.9% (McGavack *et al.*[15]). However, from existing clinical re-

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ports, which cover considerably more than 1,000 patients in the case of each drug, carbimazole seems to have produced fewer severe toxic reactions (granulocytopenic and urticarial-febrile reactions), than the former.

In view of the claims made for the longer and more intensive action of carbimazole and the lessened likelihood of side effects from its use, it was decided to have a single group of workers test the activity of each drug without knowing the identity of either, and to make such tests on a weight for weight basis.

Methods and Procedures. 1. PREPARATION AND HANDLING OF DRUG MATERIALS. Tablets of a standard size and shape containing either 5 mg. of methimazole or carbimazole were especially prepared for us by a pharmaceutical manufacturer.* One of the two compounds was labelled CT-711 and the other CT-712, but the actual identity of the material present in each instance was not made known to any of the investigators during the period of study. All tablets and the key to the identity of the same were shipped to the hospital pharmacist. The nature of each material was made known to the principal investigator after the sealing and mailing of a final report in the presence of the pharmacist, CT-711 being methimazole and CT-712, carbimazole.

In daily doses up to 20 mg., the unit dose of active material was 5 mg. With daily doses of 30, 40 and 60 mg., respectively, the unit doses were 10, 10 and 15 mg., respectively.

Maintenance doses of the preparations varied from 5 to 30 mg. daily. Most of the subjects required 15 mg. for a steady continuous effect.

2. ADJUVANT MEDICATION. As a general rule, patients were given a moderate dose of a "gunshot" vitamin or vitamin-mineral mixture; sedatives were not used, unless demanded by the patient, or the patient was previously accustomed to them.

Iodine, as Lugol's solution was given in doses of one or less minims daily to all subjects as soon as the thyrotoxicosis was brought fully under control. This was continued throughout the remainder of the treatment with the antithyroid compound and for from one to 3 months after its discontinuance.

3. SUBJECTS, PREVIOUS THERAPY AND THERAPEUTIC REGIMEN. In 123 patients, the diagnosis of hyperthyroidism was established by methods previously detailed (Beierwaltes[3], Stone, Petit and Starr[23]). Of these 123 patients, 26 were men and 97 women, whose ages ranged from 16 to 83 years with an average age of 43.8 years (Table 1). Thirty-five of these patients were hospitalized for varying periods of time, not because of the greater severity of their disease, but with a view to making more continuous and exhaustive investigation of their responses. Of these, 20 were first treated with methimazole and 15 with carbimazole.

Except in those patients who developed an untoward reaction (11 in number), each subject was kept on the initial drug for not less than 10 weeks (11 to 42 weeks) before switching to an equal amount by weight of the second preparation.

Of the 123 patients, 68 initially received methimazole, of whom 54 were later switched to carbimazole. The remaining subjects, 55 in number, first were given carbimazole. Later, 26 of them were transferred to therapy with methimazole. Thus were established a total of 203 trials of the two drugs, 94 for methimazole and 109 for carbimazole. In the case of patients first treated with methimazole, 5 were transferred to carbimazole prior to the completion of the 10-week period because of the development of toxic symptoms. One who had had no reaction to carbimazole developed a rash about 4 weeks after being transferred to treatment with methimazole. Two patients who initially received carbimazole were transferred to methimazole prior to the completion of the 10-week period because toxic manifestations appeared. In one of these, the latter drug had to be stopped as the symptoms failed to clear, even with a reduction of dose. One patient initially treated with methimazole without any untoward effects, developed pruritus and a rash about 5½ weeks after beginning therapy with carbimazole.

Of the subjects who first received methimazole, 14 were men and 54 women, with a range of age from 22 to 83 years and an average age of 43.4 years (Table 1).

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TABLE 1.—CLINICAL DATA FROM 123 THYROTOXIC PATIENTS TREATED WITH AN IMIDAZOLE

				Drug					
	Total			Methimazole			Carbimazole		
Rubric	*No. Pts.*	*Range*	*Aver.*	*No. Pts.*	*Range*	*Aver.*	*No. Pts.*	*Range*	*Aver.*
Age (Years)	123	16–83	43.8	68	22–83	43.4	55	16–78	42.4
Sex									
Male	26			14			12		
Female	99			54			43		
Initial controlling dose (mg.)									
(a) No previous treatment*	98	30–60	40.5	53	30–60	40.7	45	30–60	40.3
(b) Transferred from another A-T compound†	25	5–30	17.9	15	5–30	18.4	10	10–30	17.1
Duration of treatment when improvement first noted (Days)	98	3–21	7.2	53	3–21	7.4	45	3–14	6.8
Period necessary for control of hyperthyroidism (weeks)	98	2–11	4.6	53	2–9	4.5	45	2–11	4.7
I-Duration of treatment with initially used drug (weeks)	123	1.5–42	19.7	68	1.5–42	17.3	55	6–120	22.7
(a) All cases									
(b) Cases not previously treated with an A-T Comp.	98	1.5–42	20.1	53	1.5–42	17.3	45	3–42	23.0
(c) All cases without toxic reaction to the initially used drug	112	11–42	20.3	62	12–42	16.0	50	11–42	23.1
II—"Cures"‡	41	5–42	27.6	25	5–36	26.8	20	8–52	30.2

*Within 10 weeks of initiating the present study.
†On which patient was already euthyroid.
‡7 had only 1 drug: 3 methimazole and 4 carbimazole.

The thyroid gland was diffusely enlarged in 47 and nodular in 21. Twenty-eight of these patients had at some time received one or more other antithyroid compounds; in 15 of these the transfer was made to methimazole when the patient was euthyroid. Fifteen of the 28 had taken propylthiouracil, 18 methylthiouracil, 23 methimazole and 17 carbimazole. Two had had mild rashes one year or more prior to the present treatment while taking 30 mg. daily of methimazole, and a third an urticarial-febrile reaction to that drug. During the present trials, none of these developed a reaction to methimazole. Unfortunately, only one of them was ever given carbimazole; there was no reaction. Eight patients had had rashes from one of the thiouracils and one an urticarial-febrile reaction to propylthiouracil. In none of these patients did methimazole, or later in 4, carbimazole cause any disturbance.

Of the 55 subjects who first received carbimazole, 12 were men and 45 were women with a range of age from 16 to 73 years and an average of 42.4 years (Table 1). The thyroid gland was diffusely enlarged in 39 and nodular in 16. Seventeen of these patients had on some previous occasion received one or more other antithyroid compounds. These included propylthiouracil in 4, methylthiouracil in 5, methimazole in 13 and carbimazole in 4. One of these patients who had previously used methylthiouracil, methimazole and carbimazole had had a transient rash while taking methimazole which had disappeared with a lowering of the dose. No other compound caused any untoward effect in this subject, nor did he observe any unpleasant reaction while taking either carbimazole, or, later, methimazole, during the present double blindfold study. Three patients had had a mild skin reaction to propylthiouracil and one to methylthiouracil. None of these showed any untoward response to carbimazole.

Results. The transfer from one drug to the other had as its major purpose a direct comparison of therapeutic activity and tolerance in each particular individual. On a weight for weight basis, no difference in action could be detected by us as a result of these alternations of the two drugs. In 5 of the 8 individuals who developed a toxic effect from methimazole, there was no reaction to carbimazole, although in 3 instances a lower dose of the second drug was employed from the outset and in one of these carbimazole was not given until much later. In 2 of 6 subjects who developed a reaction to carbimazole, there was no untoward effect from the use of methimazole (See Toxic Effects). In recording data about the influence of these drugs on hyperthyroidism, we will particularly summarize the response to the first of the drugs used in each patient. Most of the observations which follow are pertinent to the initial 98 trials in people not previously treated. However, data from all other trials will be included, whenever informative. As a general rule, the second drug acted similarly to the first and afforded chiefly information regarding the incidence of toxic side effects and dosages necessary for the continuing control of the disease.

(a) OBSERVATIONS ON INITIAL IMPROVEMENT OF THE PATIENT (TABLE 1). In general, 30 mg. or more daily of the antithyroid compound were necessary to effect a prompt improvement in the individual patient's condition.

Initial improvement occurred in from 3 to 21 days with an average of 7.2 days when methimazole was used and an average of 6.8 days when carbimazole was given (Table 1). The one patient in whom definite improvement in the hyperthyroid symptoms was delayed for 21 days also had Addison's disease. Despite a basal metabolic rate only moderately elevated before treatment (plus 27%), other evidence was convincing: serum protein bound iodine of 8.7 μg. per 100 ml. and a radio-iodine uptake of 82% in 24 hours. At the end of one week of treatment for both the Addison's disease and the hyperthyroidism, the basal metabolic rate had risen to plus 57% and previously masked symptoms of Graves' disease were outspoken. If this case is left out of the calculations, then the average time for "first im-

provement" with methimazole becomes 6.9 days with a range from 3 to 14 days. With each of the drugs, there was not infrequently a general impression of subjective improvement within 24 to 48 hours. However, if this could not be readily identified by the patient with a change for the better in some specific symptom or symptoms, his condition was not recorded as improved.

(b) TIME NECESSARY TO CONTROL THE THYROTOXIC STATE (TABLE 1). In the 53 patients who received methimazole and had not within 2 months had any other antithyroid compound for the current attack, it took an average of 4.5 weeks to control all of the manifestations of the disease, with a range of from 2 to 9 weeks. Corresponding figures for the 45 patients who were initially given methimazole were 4.7 weeks, with a range of from 2 to 11 weeks.

(c) DOSAGES (TABLES 1 AND 2). Throughout the study, the two drugs proved to be equally active on a weight for weight basis. Initially effective doses (Table 1) ranged from 30 to 60 mg. daily for each drug with an average daily dose of 40.7 mg. for methimazole and of 40.3 mg. for carbimazole. Prompt control was never attained with 20 mg. daily. Forty milligrams was usually satisfactory and in the last 54 cases, treatment was routinely started with this amount daily. In 6 cases taking methimazole this was raised to 60 mg. daily for one, one, one, two and three weeks, respectively, in order to achieve an initial response. In 5 instances, the 40 mg. dose was tried for one week only before the increase was made and in the sixth instance an unsuccessful 3-weeks' trial had been made. With carbimazole, 5 patients were raised from the 40- to 60-mg. dose at the end of one week during which no change in status had been observed; in both, it was possible to resume the previous dose at the end of one week as an initial response had been noted. In one patient receiving carbimazole, the initial dose was 60 mg. daily. This patient was highly thyrotoxic, had been mistakenly diagnosed as a neurotic with menstrual difficulties, and had received a wide variety of misdirected therapies as a result. Since the early establishment of confidence was important, it was decided to use at the outset the largest dose we considered relatively safe. Perhaps a smaller dose would have been rapidly

TABLE 2.—INITIAL DOSES OF METHIMAZOLE OR CARBIMAZOLE IN THE MANAGEMENT OF 98 THYROTOXIC PATIENTS

Drug	*Total No. Subjects*	*No. Subjects at Daily Dose (mg.)*			
		60	*40*	*30*	*20*
Methimazole	53		47 (1)	4	2 (2)
Carbimazole	45	1	35 (3)	5	4 (4)
Totals	98	1	82	9	6

(1) In 5 patients, this dose was raised to 60 mg. after one week and in a sixth patient after 3 weeks. In 4 cases, the 60 mg. dose was used for 1 week; in one for 2 weeks and in the sixth instance for 3 weeks.
(2) In neither subject was this dose satisfactory. After 10 days in one and 2 weeks in the other, it was increased to 30 mg. with good results.
(3) In 5 subjects, after 1 week, this dose was raised to 60 mg. for 1 week and then returned to the former level.
(4) Not effective in any instance after 2 weeks, and then increased in 2 to 30 mg. and in 2 to 40 mg. before rapid control could be effected.

and even equally rapidly effective. In any event, a dramatic change in subjective symptoms was present at the end of one week.

Forty-five of the 123 patients involved in the present study had previously received one or more of the thiouracils or an imidazole or both. Their previous behavior while taking known imidazoles is in consonance with our conclusion from the present study that these drugs can be used interchangeably on a weight for weight basis. As far as the thiouracils are concerned, the data indicate that propylthiouracil and methylthiouracil, on a weight for weight basis, are about one-tenth as active as either of the two imidazoles under investigation.

(d) DURATION OF TREATMENT (TABLE 1). The length of treatment of the 123 cases on the originally used material averaged 19.7 weeks with a range of from 1.5 to 42 weeks. There were 3 patients on methimazole treated less than 3 weeks that were transferred to carbimazole because of a toxic reaction and one receiving carbimazole less than 4 weeks, who was transferred to methimazole for the same reason. If we exclude these and all other cases having a toxic reaction, then the period of treatment varied for methimazole from 12 to 42 weeks, and for carbimazole from 11 to 42 weeks.

In the 98 patients who had not had any previous treatment for the current thyrotoxic attack, the average duration of treatment was 20.1 weeks, with a range from 1.5 to 42 weeks (Table 1).

In the absence of a toxic reaction, no "switches" to the second drug were made prior to the end of the tenth week of therapy. This was done because in our experience, most of the unfavorable reactions to these drugs have been seen within such a period of time. Urticarial-febrile reactions usually occur within the first 3 weeks. Local and generalized rashes of other types and bone marrow reactions may occur at any time. However, the bone marrow depression is most common between the fifth and eighth weeks of treatment. The end of the tenth week was therefore elected as a minimum time for changing from one drug to the other. At the time of this analysis, the 54 patients transferred from methimazole to carbimazole had received the second drug for periods of time varying from 1.5 to 36 weeks, with an average of 24.1 weeks. Twenty-six patients originally given carbimazole and later changed to treatment with methimazole have been on the latter drug for periods of time varying from 1.5 to 20 weeks, with an average of 11.4 weeks. In these 80 "transferred" patients the maintenance doses have ranged from 5 to 30 mg. daily and are the same as maintenance doses of the initially employed drug.

The word "cure" (Table 1) is used in a specific sense here. If the patient was able to go without medicine for 16 weeks or more, he or she was considered cured. Any return of symptoms subsequent to that time was looked upon as a recurrence and not a relapse. Using this perhaps somewhat arbitrary definition, we find that 25 patients who received methimazole can be listed as cured after an average of 26.8 weeks of treatment, with a range of from 5 to 36 weeks, and 20 who received carbimazole can be similarly listed after an average of 30.2 weeks of treatment with a range from 8 to 52 weeks.

(e) CLINICAL MANIFESTATIONS (TABLES 3 AND 4). The subjective manifestations and physical findings in the cases here studied were for the most part classical for Graves' disease or toxic nodular goiter. These manifestations receded with rather orderly regularity as a result of therapy and no

TABLE 8.—CHANGES IN THE CLINICAL MANIFESTATIONS OF HYPERTHYROIDISM DURING TREATMENT OF 53 PATIENTS WITH METHIMAZOLE AND 45 PATIENTS WITH CARBIMAZOLE

	Methimazole				*Carbimazole*			
	Before		*After*		*Before*		*After*	
Clinical Finding	*Range*	*Aver.*	*Range*	*Aver.*	*Range*	*Aver.*	*Range*	*Aver.*
Weight (lbs.)	98–180	131.3	103–192	146.7	103–190	137.4	111–181	148.8
Pulse (Beats/min.)	80–164	110.4	60–108	79.1	80–168	125.0	64–128*	81.5
Blood Pressure (mm.Hg)								
Systolic	112–188	138.3	100–138	116.9	102–188	146.2	96–146	122.4
Diastolic	20– 88	58.7	50– 80	72.3	32–110	67.4	60– 90	7.6
Basal Metabolic Rate (%)	+20 to +84	49.2	−16 to +18	+0.8	+18 to +81	+55.6	−12 to +33	+4.3

*This value is the only one above 100 beats/min. after treatment; drug was stopped when patient developed urticarial-febrile reaction on 12th day. Average rate includes this case; without it the value is 80.4.

sharp distinctions could be detected between the influence of the two drugs. In Table 3 we have set down the analysis of 4 manifestations which have been routinely checked in all patients at every visit. The data speak for themselves:

1) *Weight (Table 3).* In the 53 patients given methimazole initially, an average gain in weight of 13.4 pounds was effected. Two patients actually lost 4 and 2 pounds respectively, and 3 remained at the same weight, despite the maintenance of a euthyroid state. The actual amount gained by other patients varied from one to 26 pounds.

The average gain in weight achieved by the 45 patients who received carbimazole initially was 11.4 pounds. Five subjects lost weight; 2 of these were attempting to do so; 2 others were diabetic and not well controlled during part of the observed period because of emotional problems. Two patients remained at the same weight throughout the period of treatment. The amount gained by the remainder of the subjects varied from 6 to 28 pounds.

2) *Pulse rate (Tables 3 and 4).* A reduction in pulse rate is the rule when the thyrotoxic state is treated with an antithyroid compound. Under the influence of methimazole the average rate per minute changed from 110.4 to 79.1; corresponding figures for carbimazole were 125.0 and 81.5 (Table 3). If we classify the "before" and "after" pulse rates into three categories, the change becomes even more striking (Table 4). In 44 of 53 subjects receiving methimazole, the pulse rate was above 100 per minute before treatment; it remained so in only 2 of these at the end of the period of treatment. Thirty-seven of the 53 subjects given methimazole showed final pulse rates under 80 as compared with none in this category before treatment.

Thirty-seven of 45 subjects given carbimazole had pulse rates above 100 at the beginning of treatment and only two at the end of the period of observation. None showed a pulse rate below 80 before therapy and 21 did afterwards (Table 4).

TABLE 4.—CHANGES IN PULSE RATE AS A RESULT OF TREATMENT WITH METHIMAZOLE AND CARBIMAZOLE

Drug and Period	*Range (Beats/min.)*	*Total No. Cases*	*No. Cases with Pulse Beats per Minute*		
			Above 100	*Between 80 & 99*	*Below 80*
Methimazole					
Before treatment	80–164	53	44	9	0
After treatment	60–108	53	2	14	37
Carbimazole					
Before treatment	80–160	45	37	8	0
After treatment	64–112	45	2	22	21

3) *Blood pressure (Table 3).* The administration of methimazole to 53 individuals was accompanied by an average decrease in systolic blood pressure of 21.4 mm. Hg. The use of carbimazole in 45 patients was accompanied by an average decrease in systolic blood pressure of 23.8 mm. Hg. Diastolic pressures were slightly elevated by each of the two drugs (Table 3).

In 7 patients given methimazole, the initial systolic blood pressures exceeded 150 mm. Hg and in an additional 23 subjects it lay between 130 and 150 mm. Hg. Pressures in these two

groups were usually lower after treatment and all of those originally above 150 were 130 or below at the end of the therapeutic period.

In 4 patients who received carbimazole, systolic blood pressures initially above 150 mm. Hg were reduced to values of 130 or below as a result of treatment.

4) *Basal metabolic rate (Table 3).* The levels for the basal metabolic rates in the 98 patients who were first treated by one of the two compounds under investigation are shown in Table 3 and correspond roughly with the clinical findings.

5) *Other laboratory data.* In general, the basal metabolic rate was a satisfactory guide to the condition of the patient and was performed routinely in relation to each visit of the patient. However, if in doubt some other test was also carried out. With this in mind, initial values for serum cholesterol were obtained in all patients and serum protein bound iodine and 24-hour thyroidal radio-iodine uptakes were in 24 and 38 subjects, respectively. With 6 exceptions, the values for radio-iodine uptake were above 55% and no value fell below 48%. Radio-active iodine uptakes were not repeated in any subject. Prior to treatment, only three of the values for serum protein bound iodine were below 8.5%. Serum protein bound iodine values were repeated in 15 subjects after full control was established and were found to be within the normal limits.

Initially none of the cholesterol values were above 250 mg. per 100 ml. and 24 were below 170 mg. per 100 ml. The mode for values in our laboratory lies between 180 and 230 mg. per 100 ml. Values in 23 of the controlled cases were above 250 mg. per 100 ml. and only one post-treatment figure was below 170 mg. per 100 ml.

(f) UNTOWARD EFFECTS (TABLE 5). Eight reactions occurred with 94 trials with methimazole in as many patients. Six such reactions appeared in the course of 109 trials with carbimazole.

With methimazole in 94 trials, there were two urticarial-febrile types of reaction (Cases 27 and 99), one of which was mild and the other severe. They occurred on the 12th and 10th days respectively of drug administration. At no time was the first patient (Case 27) particularly ill, although most uncomfortable with the intense generalized pruritus and urticaria (Table 5). The second patient felt and looked sick, but responded nicely to large doses of an antihistaminic and relatively large doses of prednisone. In the first instance, major symptoms were relieved within 5 days, while in the second, this took 10 days. It is interesting to note that the daily dose of drug when each of these reactions occurred was 60 mg. We have usually considered urticarial-febrile reactions to be of an allergic nature and more or less independent of dosage. However, both of the above-mentioned reactions appeared while large doses were being employed, albeit for relatively short periods of time. The drug carbimazole was tolerated without any side effects in the patient with the milder of these reactions in a daily dose of 20 mg., as was also methimazole in doses up to 30 mg. The more severe reaction (Case 99) was mimicked when 20 mg. of carbimazole were used for 4 days, although the course of this response was not so rigorous as that originally developed by the first-used drug.

Pruritus, rash or edema or some combination of these symptoms was present in 6 patients treated with methimazole (Cases 1, 7, 56, 61, 73 and 104, Table 5). In 2 of these (Cases 1 and 56) the reaction disappeared while the drug was continued at a lower level of dosage, 20 mg. daily

TABLE 5.—TOXIC EFFECTS IN 109 PATIENTS TAKING ANTITHYROID COMPOUNDS METHIMAZOLE AND CARBIMAZOLE

Case No.	Age (Yrs)	Sex	Type of reaction	Day of appearance	Dose (mg.) Daily Initial	Dose (mg.) Daily At time of reaction	Dose (mg.) Total	Comments
Methimazole								
	44	F	Pruritus and rash extremities	36	15 × 4	10 × 3	1290	Disappeared when daily dose was decreased to 20 mg. Later, no reaction to carbimazole in 15 to 30 mg. daily.
7	27	F	Generalized pruritus	13	10 × 4	10 × 4	520	Patient was switched to carbimazole, 30 mg. daily following which symptoms disappeared.
27	37	F	Urticaria and fever	12	15 × 4	15 × 4	720	Highest temp. 100.2° F.; symptoms subsided in 5 days, Five days thereafter dose of 30 mg. daily taken without return of toxic reaction. Later no reaction to carbimazole while taking 20 mg. daily.
56	45	F	Generalized pruritus and rash. Edema of extremities.	27	10 × 3	10 × 3	810	Patient had used carbimazole for 14 weeks without any untoward effects. Maintenance dose high; however, eventually controlled on 20 mg. daily without side effects.
73	34	F	Generalized pruritus; slight edema about ankles	17	10 × 4	10 × 3	640	Drug was stopped. Itching subsided within 4 days but reappeared after resuming methimazole for 2 days. Switched to carbimazole at same level of dose; no reaction.
99	36	F	Urticaria and fever	10	15 × 4	15 × 4	600	The most severe reaction encountered with temp. 104°, nausea, vomiting, widespread urticaria; 10 days to subside with aid of antihistaminics, cortisone, etc. Similar but less severe reaction to carbimazole on 30 mg. daily.
Carbimazole								
40	36	M	Rash, rt. leg	13	5 × 4	5 × 4	260	No reaction to methimazole, even larger dose.
61	28	F	Generalized pruritus, localized rash and edema	24	10 × 4	10 × 3	790	Drug stopped 7 days. Pruritus beginning second day on attempting to re-employ. Similar reaction to methimazole in same dosage.
103	39	F	Generalized pruritus	39	15 × 4	10 × 3	1380	Subsided as soon as dose was reduced to 20 mg. daily. Previously no reaction to methimazole in similar doses.
140	56	F	Rash—legs	14	10 × 4	10 × 4	560	Similar mild reaction later to methimazole 30 mg. daily.
128	34	F	Rash—legs with ankle edema	28	10 × 4 15 × 4	10 × 3	1330	No reaction to methimazole later. Had had more severe reaction to propylthiouracil previously.

rather than the preceding 30 mg. One patient (Case 7) was transferred to treatment with carbimazole at a lower level of dosage, 30 instead of 40 mg. daily, with complete subsidence of symptoms. It is unfortunate that a simple lowering of the level of dose of methimazole was not tried in this instance. In 2 subjects, discontinuance of the drug temporarily relieved the condition but attempts to resume it reproduced the untoward manifestations. In one instance, it was possible later to employ carbimazole at the same level of dosage without any ill effects. In the fifth and sixth cases, the initial reaction had occurred while taking carbimazole, but neither this drug nor methimazole was later tolerated in any effective dose.

With carbimazole, 6 toxic reactions appeared in 6 of 109 patients receiving the drug. One of these was an urticarial-febrile reaction in a patient who had had a similar response to methimazole (Case 99). The second patient (Case 61) developed generalized pruritus, a localized rash and localized edema about the 24th day of treatment. This subsided but returned on the second day after attempting to use the drug again at the same level of dosage. A similar response was attendant upon the use of methimazole a few days after the second reaction had subsided. In a third patient (Case 103) a generalized intense pruritus appeared on the 39th day of treatment. The dose of drug was reduced from 30 to 20 mg. daily, and the entire reaction subsided while the drug was continued. Previously, this patient had received methimazole in similar doses for 20 weeks without any untoward effect of any kind. In 2 patients (Cases 40 and 104) rashes appeared transiently over the lower extremities, while 20 and 40 mg., respectively of carbimazole were being administered daily. Both disappeared without discontinuing the drug, and in the former, methimazole was later tolerated without incident. The sixth (Case 128) and final patient with a reaction to carbimazole developed a slight ankle edema and rash over the legs which appeared on the 28th day of treatment, when a total of 1,330 mg. had been received. This disappeared without a reduction of dose. Later, methimazole was employed at similar levels of dosage without untoward incident.

There was no instance in the entire 203 trials extending over periods of time up to nearly a year that a bone marrow reaction was observed. It may be said that we did see a reduction of polymorphonuclear cells to 30% with normal total white counts (above 6000 per c.mm.) and total white counts around 3500 per c.mm. with the percentage of polymorphonuclear cells normal (above 60%). However, these were transient reactions, as proven by quite normal blood counts 12 to 24 hours following those in which an abnormal finding was elicited.

Summary and Conclusion. 1. Methimazole and carbimazole, identified by the unknown code numbers only, have been administered to 123 patients in a series of 203 trials. Methimazole was given initially to 68 patients and carbimazole initially to 55 patients.

2. The influence of each of the two preparations has been described in relation to the rapidity and the completeness of control, the dosages used, and alterations in a variety of clinical manifestations.

3. The two preparations appeared to be equally effective, on a weight for weight basis, in controlling the manifestations of hyperthyroidism.

4. Eight toxic reactions were encountered during the administration of methimazole, 6 with carbimazole. Two of these in association with the use of

methimazole were urticarial-febrile reactions. All remaining reactions were manifested by one or a combination of the following features: pruritus, localized rashes, and transient edema.

5. It is concluded that both methimazole and carbimazole are effective thyroid blocking agents of approximately equal activity. Methimazole may be more toxic than carbimazole, but a good many more cases should be studied before a hard-and-fast conclusion is drawn regarding this statement, as the differences in the present study are not statistically significant.

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(Interlingua on page 38)

OBSERVATIONS ON THE EFFECTS OF EXPOSURE TO NERVE GAS
I. CLINICAL OBSERVATIONS AND CHOLINESTERASE DEPRESSION

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and

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Preliminary reports have indicated that anticholinesterase agents may be useful in quantitating erythrocyte survival and production. Cohen and Warringa[2] tagged red cells with P_{32}-labeled diisopropylfluorophosphate (DFP). Estimates of the survival times in their 2 cases and in 3 additional cases (Mayer and Ley[10]) agree with survival times of red cells as calculated by other methods. Samuels, Reinhart, Jelinck, and Furrer[12] suggested that the regeneration of red blood cell cholinesterase activity (RBC-ChE) following the administration of DFP might be used to evaluate erythrocyte production. Each suggestion would imply that both survival and production could be simultaneously estimated by the administration of DFP, part of which would be labeled with P_{32}. Before this ultimate goal is achieved more fundamental knowledge is needed in respect to the recovery of RBC-ChE.

The observation of RBC-ChE depression and recovery following accidental exposure to nerve gas ("G" agents) afforded an excellent opportunity to study this problem. The nerve gases belong to the group of organic esters of phosphoric acid derivatives which are known as anticholinesterase agents. Parathion, DFP, tetraethyl pyrophosphate (TEPP) are related to nerve gases and have similar anticholinesterase activity. The signs and symptoms of intoxication, attributable to the accumulation of acetylcholine in the effector organs, have been well described in the literature (Comroe, Todd and Koelle[3], Freeman and Epstein[4], Grob *et al.*[5-9]). Most of the clinical observations have been limited to the more advanced signs and symptoms and do not include the early minor manifestations noted in the present paper.

In vitro and *in vivo* parathion, DFP, and TEPP inactivate plasma sooner than RBC-ChE. In contrast RBC-ChE is more sensitive than plasma ChE to the effects of nerve gases. The recovery of RBC-ChE is described in detail in another paper (Woodson and Craig[14]).

Methods. All ChE determinations were done by the method of Michel[11]. A micro-adaptation was developed by Stubbs and

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Fales[13] to permit the use of finger capillary blood. The blood was drawn into a heparin coated melting point tube by capillary action, one end sealed, and the tubes centrifuged. The tubes were then broken at the junction of the plasma and red cells and a 0.1 ml. sample from each end was used for the determination of ChE activity.

All the cases in the present study were seen and examined by a medical officer immediately after exposure. One of us (A.B.C.) saw many of the cases originally and reexamined every subject within 12 hours of exposure. He followed each subject for the remainder of the subject's time of recovery. No cases received any specific treatment.

Results. CLINICAL OBSERVATIONS. Nine men (cases 1 to 9) were exposed to nerve gas vapor while testing a new type of gas mask. Erythrocyte cholinesterase depression was due to cutaneous absorption. One man noted rhinorrhea at the time of the test and was observed to have unilateral miosis. All other subjects were symptom-free and showed no miosis at the conclusion of the test. Their symptoms were reported when seen 2 days later. Three men had no symptoms. Three had experienced definite hyperhidrosis and one thought that he had perspired a little more readily than usual for a day after the test. Another had diarrhea and noticed pronounced irritability for 2 days. Both complaints were quite unusual for this man.

The next 6 men (cases 10 to 15) developed symptoms of minor intoxication due to accidental vapor exposure of the eyes and respiratory tract. All exhibited miosis and 4 complained of dim vision and impaired accommodation. Four experienced rhinorrhea and complained of tightness of the chest. In each instance contact with the agent was so brief as to preclude any significant cutaneous absorption.

In contrast, cases 16 to 19 complained of hyperhidrosis in addition to the usual eye and respiratory symptoms. These men were exposed during an accidental spill of liquid agent and exposure of the skin to liquid or high vapor concentration, or both, occurred because of defective protective clothing.

Case 20 voluntarily participated in a carefully controlled experimental exposure of a limited skin area to liquid agent. The only manifestation of exposure was hyperhidrosis over the area of application of agent.

The exact circumstances of the exposure of cases 21 and 22 were not known but it is likely that the RBC-ChE depression was due to absorption of the agent through the skin of the hands. One of these men had no symptoms but the other presented mild mental confusion and incoordination.

RBC-ChE DEPRESSION. The individual RBC-ChE data are given in Table 1. In this series the depression of the RBC-ChE ranged from 14 to 81% of the control values. The median depression of the group was 61%, the mean 53% of the control values.

PLASMA ChE. From Fig. 1 it is obvious that the RBC-ChE is more sensitive than plasma ChE to the effects of nerve gases. Although there is a wide scatter, a regression was calculated from this series. It would appear that the plasma ChE would not be expected to show depression until the RBC-ChE had been reduced about 20% below normal. Thereafter, the RBC-ChE is about 1.3 times more sensitive than plasma ChE (confidence limits 1.15 to 1.47 at p .05). *In vitro* results also indicate that RBC-ChE is more sensitive than plasma ChE to the anticholinesterase effects of nerve gas (Grob and Harvey[7]).

CLINICAL CORRELATION. In our experience only about 15% of subjects exhibiting minor intoxication to nerve gas had depression of the RBC-ChE. Of those who did have ChE depression

TABLE 1.—ERYTHROCYTE AND PLASMA ChE OF SUBJECTS EXPOSED TO NERVE GAS

	Average Control ChE			*Initial ChE After Exposure*	
Subject	*RBC pH/hr.*	*Plasma Δ pH/hr.*	*No. det'n.*	*RBC Δ pH/hr.*	*Plasma Δ pH/hr.*
1	.63	.61	4	.48	.60
2	.75	.99	3	.53	.84
3	.75	.96	6	.54	.89
4	.69	.69	6	.35	.56
5	.63	.80	6	.49	.69
6	.74	.66	6	.42	.60
7	.75	1.02	3	.60	1.20
8	.82	.91	5	.69	.75
9	.74	.97	4	.63	1.02
10	.72	.58	5	.27	.29
11	.75	1.10	7	.50	.81
12	.78	.79	4	.57	.53
13	.75	.78	3	.61	.74
14	.81	.79	5	.57	.77
15	.77	.92	2	.38	.61
16	.75	.73	12	.47	.60
17	.85	.82	9	.29	.59
18	.75	.88	9	.21	.55
19	.74	.87	10	.41	.73
20	.70	.89	3	.46	.78
21	.61	.77	5	.05	.76
22	.74	.86	4	.13	.85

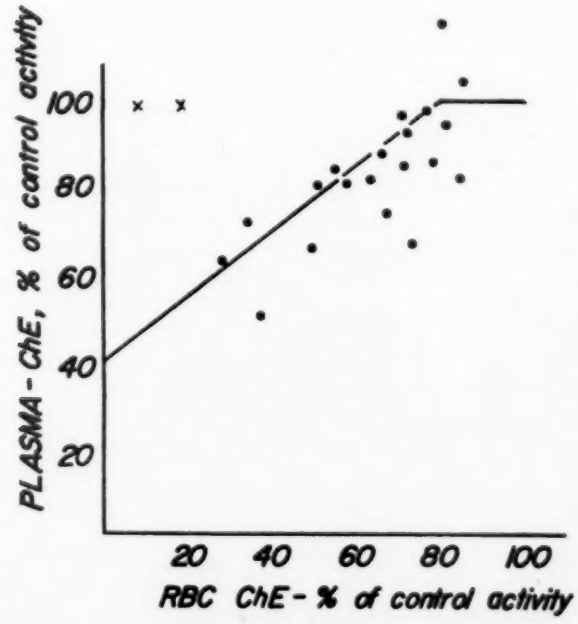

Fig. 1.—Relationship of plasma and RBC-ChE depression caused by nerve gas.

most had evidence of cutaneous absorption.

In this series the correlation between the clinical manifestations of exposure and the degree of ChE depression is possible only in the most general way. The average RBC-ChE of the first 9 cases was 66% of control levels. Three men had no symptoms and 5 experienced minor symptoms appreciated only in retrospect. One man showed evidence that his mask had leaked and was the only subject who had any objective signs of exposure. All of the next 6 subjects (cases 10 to 15) had objective and subjective evidence of exposure and the average RBC-ChE after exposure was 60%. In general the next 4 men (cases 16 to 19) had more symptoms per man than the other cases. The average RBC-ChE of these 4 was 46% of normal.

Within each group there were such wide variations that it was impossible to correlate individual RBC-ChE depression with the status of the subject. Cases 21 and 22 demonstrated the most severe RBC-ChE depression of the entire series. Case 21 experienced signs and symptoms of moderate intoxication, but case 22 was discovered only because of his association with case 21. The plasma ChE of both of these men was not depressed at any time during observation. Because the plasma ChE was unaffected, it was suspected that exposure was chronic in nature, that is, plasma ChE failed to show a cumulative dosage effect because of the fast recovery of plasma ChE.

Discussion. The clinical observations made on this group of subjects are similar to those made by others. It is not surprising that there is a lack of correlation between the clinical picture of minor exposure and the degree of RBC-ChE depression in any one individual. Observations of other cases have led us to believe that the early respiratory symptoms of thoracic pressure may be largely irritative phenomena and that rhinorrhea and eye symptoms represent local exposure. Erythrocyte cholinesterase depression depends upon systemic absorption of the agent. This series of patients represents about 15% of all cases of minor intoxication. Three-fourths of the subjects showing RBC-ChE depression had definite evidence of skin absorption. Most of the cases with no detectable RBC-ChE depression were the result of brief exposure to agent vapor without protective devices. The brevity of contact was due to the subject's previous training and awareness of the meaning of their symptoms. This does not imply that RBC-ChE depression is not possible by respiratory tract exposure. The experience has been that respiratory and ocular symptoms will usually become manifest before RBC-ChE depression has occurred; but if these routes of absorption are protected, as by a gas mask, it is still possible to produce RBC-ChE depression by cutaneous absorption.

The observation that the RBC-ChE is more sensitive than plasma ChE to the effects of nerve gas confirms previous statements (Grob and Harvey[7]). Quantitation of the relationship may be helpful in comparing the effects of nerve gas on ChE with the effects of DFP to which the plasma ChE is more sensitive. These differences are unexplained at present. Perhaps we are dealing with different cholinesterases with different affinities for the various anticholinesterase agents (Bodansky[1]).

Summary. The clinical observations of nerve gas intoxication were presented from our experience with 22 cases who also demonstrated depression of the red blood cell cholinesterase activity. The anticholinesterase properties of this agent, which is related to certain insecticides, are man-

ifested by a greater reduction of the cholinesterase activity of the red blood cells than of plasma. Clinical signs and symptoms depend more on the route of adsorption than the amount which is reflected by the degree of depression of the red blood cell cholinesterase activity. Although there is a general direct relationship between the clinical picture and the depression of cholinesterase activity, correlation is not possible in any single case.

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SUMMARIO IN INTERLINGUA

Observationes Super le Effectos de Exposition a Gases Neurotrope
I. Observationes Clinic e Depression de Cholinesterase

Es presentate observationes clinic in intoxication per gases neurotrope super le base de nostre experientias con 22 casos characterisate etiam per depression del activitate de cholinesterase del erythrocytos. Le proprietates anticholinesteratic del agente in question, que es relationate a certe insecticidas, se manifesta per un plus grande reduction del activitate de cholinesterase in le erythrocytos que in le plasma. Le signos e symptomas clinic depende plus del via de absorption que del quantitate absorbite in tanto que isto es reflectite per le grado de depression del activitate de cholinesterase in le erythrocytos. Ben que il existe in general un relation directe inter le aspecto clinic e le depression del activitate de cholinesterase, nulle correlation pote esser postulate pro le caso individual.

GAMMA GLOBULIN IN THE MANAGEMENT OF ASTHMA ASSOCIATED WITH INFECTION

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The problem of asthma repeatedly precipitated by, or associated with, respiratory infection is a common one. Although frequently observed in adult asthmatics, this situation is somewhat more prominent in young children. In many cases, careful study reveals specific extrinsic allergic factors, which when controlled reduce the asthmatic episodes, even in the face of frequent "colds." There are, however, situations where despite all reasonable anti-allergic efforts, persistent difficulty in association with repeated respiratory infection continues.

The prophylactic administration of pooled gamma globulin is one of many types of treatment suggested for the control of these cases of so-called "infectious asthma." Although the use of gamma globulin is often mentioned, very little in the way of documented experience has appeared in the literature. One of the most frequently quoted references is a report read by Bowen at a meeting of the American Academy of Allergy in 1955[2]. In an abstract of this paper, the author states that "gamma globulin plays a positive and beneficial role by affording the asthmatic child better resistance to respiratory infection as compared with a control group." In a general article on the symptomatic treatment of asthma in children, Overall[11] noted good results in "infectious asthma" when gamma globulin is given in doses of 1 to 2 ml. per 10 lbs. of body weight at intervals of 3 to 4 weeks. A more recent appraisal of this type of therapy utilizing the double-blind technique was reported by Abernathy, Strem and Good[1]. These workers failed to observe any significant difference between a group of asthmatic children who received 0.6 ml. of gamma globulin per kg. of body weight at monthly intervals, and a comparable control group receiving placebo therapy. Another study of this form of treatment was initiated by the Committee on Drugs of the American Academy of Allergy with the intention of pooling the experience of a number of qualified investigators. An interim report indicated apparent benefit in some cases, and none in others (Friedlaender[7]). The data suggested that doses of at least 0.3 ml. per kg. of body weight produced the greatest number of satisfactory results.

Clinical Observations. The current report covers experiences on the administration of

pooled gamma globulin* to 11 boys and 4 girls, ages 3 to 11 years, for periods of 8 to 14 months (Table 1). Children were selected for study because the large doses of gamma globulin, calculated on a weight basis, would be most impractical to administer intramuscularly in the case of adults. Further there has been some speculation that passively supplied antibody may be more effective against systemic than against their attacks of asthma. All had been thoroughly studied from the allergic viewpoint, and had been observed during a year or more of allergic management, consisting of hyposensitization, bacterial vaccines, environmental and dietary control. Familial history of atopy was present in 13 patients, and collateral personal allergy, principally eczema and rhinitis, was recorded in 8 cases. All but 2 patients gave strongly positive

TABLE 1.—GAMMA GLOBULIN STUDY. CLINICAL DATA

Patient No. Initials	*Age Years*	*Sex*	*Familial Atopy*	*Duration of Asthma Years*	*Collateral Allergy*	*Positive Skin Tests*
1. D.M.	4	M	Yes	3½	Nasal	Negative
2. D.S.	6	M	Yes	4	No	Inhalants
3. M.S.	6	F	Yes	5	Nasal	Inhalants
4. C.G.	7	F	Yes	4	Nasal	Inhalants Foods
5. B.M.	7	M	Yes	6	Skin Nasal	Inhalants
6. J.O.	7	M	Yes	6½	Skin Nasal	Inhalants Foods
7. R.G.	11	M	Yes	5	Skin Nasal	Inhalants
8. G.K.	8	F	No	6	No	Inhalants
8. G.B.	4	M	Yes	3	Skin Nasal	Inhalants Foods
10. R.P.	7	M	Yes	6½	No	Inhalants
11. D.A.	3	M	Yes	2½	Skin Nasal	Inhalants Foods
12. S.S.	6	M	Yes	5	No	Inhalants
13. M.M.	4	F	Yes	2	Skin	Inhalants Foods
14 R.S.	4	M	Yes	3½	No	Inhalants
15. M.P.	3	M	No	2	No	Negative

local infection of mucous membranes of the upper respiratory tract (Jackson, Dowling and Anderson[10]). Systemic symptoms associated with the common cold occur more frequently in the case of children than in adults.

Each of the patients included in this study presented a similar history of asthma and frequent episodes of upper respiratory infection, which appeared to be a major factor in scratch test reactions to common inhalants or foods.

During the period of study, a daily record of asthma and respiratory infection was kept by each parent on a specially prepared data card. These records were used as a basis for comparison with an equivalent period of time prior to the course of gamma globulin. All other treatment measures were continued

*The pooled gamma globulin used in this study was generously supplied by Dr. Paul W. Yost, Assistant Director, Blood Program, The American National Red Cross, in connection with the evaluation program of the Committee on Drugs of the American Academy of Allergy.

as before. The need for antibiotics, bronchodilators, steroids, and so forth, during the control and treatment periods was noted, and also used as a basis for evaluation.

Dosage at the outset of the program ranged from 0.05 to 0.2 ml. per kg. of body weight intramuscularly every 2 weeks. Because of generally indifferent results at the end of 2 months, this schedule was increased to at least 0.3 ml. and up to 0.5 ml. per kg. every 3 weeks, except in 2 patients (cases 1 and 3) who appeared to achieve some benefit at the initially lower levels.

period occurred in 2 other patients (cases 7 and 14).

The benefit in 3 instances (cases 4, 8, and 12) was considered questionable. In each of these children, the parent was of the opinion that the youngster had improved during the treatment period. Objective evaluation based on the number of days of asthma, frequency of upper respiratory

TABLE 2.—GAMMA GLOBULIN STUDY. CLINICAL RESULTS

Patient	*Treatment period Months*	*Dose of gamma globulin ml./kg. body weight*	*Pre-treatment serum gamma globulin level*	*Result*
1. D.M.	12	0.15	low	good
2. D.S.	14	0.50	normal	good
3. M.B.	14	0.20	normal	good
4. G.G.	12	0.30	normal	questionable
5. B.M.	12	0.30	low	good
6. J.O.	14	0.30	——	good
7. R.G.	12	0.30	normal	moderate
8. G.K.	14	0.30	normal	questionable
9. G.B.	10	0.50	low	good
10. R.P.	10	0.50	——	poor
11. D.A.	8	0.50	——	poor
12. S.S.	10	0.50	high	questionabl
13. M.M.	10	0.50	high	poor
14. R.S.	14	0.30	low	moderate
15. M.P.	9	0.50	——	poor

Results (Table 2). Marked reduction in frequency of upper respiratory infection and subsequent episodes of asthma during the treatment period was recorded in 6 patients (cases 1, 2, 3, 5, 6, and 9). In 2 of these children the dose of gamma globulin was less than 0.3 ml. per kg.; 2 others received 0.3 ml. and 2 had been given 0.5 ml. per kg. of body weight.

Somewhat less, but still quite definite improvement during the treatment infection, and the requirements for symptomatic medication, did not support these conclusions.

In 4 patients (cases 10, 11, 13, and 15), no apparent benefit either as to the frequency of colds, or the severity of asthma was recorded.

Methods. ELECTROPHORETIC AND IMMUNOCHEMICAL STUDIES. Wherever possible, blood samples were drawn before starting treatment, and from 3 to 7 days after administration of a single dose of gamma globulin. All serum

samples were first studied by means of paper electrophoresis to determine any gross abnormalities. Immunochemical analyses were conducted to determine exact quantitative amounts of gamma globulin present.

Paper Electrophoresis. Electrophoretic determinations were performed on filter paper, by the method of Durrum[6] as adapted for use with the Spinco Model R. electrophoretic apparatus. Either 0.008 or 0.10 ml. amounts of undiluted serum samples were placed on Whitman 3 mm. paper strips and separated at 5 milliamperes, constant current, for 16 hours using veronal buffer, ionic strength, 0.05. After separation, strips were dried, stained with bromphenol blue (0.1%) containing 3.1% zinc sulphate. The stained, dried strips were then analyzed in the Spinco analytical, and percentages of serum components determined.

Immunochemical Determination°. Absolute concentrations of gamma globulin present in these serum samples, were determined by the immunochemical method of antigen assay as devised by Goodman *et al.*[9]. Antisera against highly purified human gamma globulin (Fr's V and II) were prepared in chickens. Serological reactions were carried out in a medium of 8.0% NaCl containing 0.01 M pH 7 phosphate buffer and 0.01% merthiolate. Reactions were set up using 0.4 ml. and 0.2 ml. quantities of 1/100 dilution of the serum sample. These aliquots were mixed with 0.7 ml. portions of fixed dilutions of anti-human gamma globulin serum and total volumes adjusted to 1.1 ml. The opacities of the resulting precipitates were read at 450 mμ in the Coleman Junior spectrophotometer after 15 minutes incubation at room temperature.

A calibration curve for the anti-gamma globulin serum was prepared by relating optical density units of turbidity of precipitates to measured amounts (micrograms) of purified gamma globulin. Turbidities of serum sample-antiglobulin precipitates were converted into known amounts of gamma globulin by comparison with the calibration curve.

Results (Tables 3 and 4). The values for serum components as determined by paper electrophoresis in pretreated individuals were generally within the limits reported as normal (Reiner, Fenichel and Stern[12], Sehon, Harter and Rose[13]). Exceptions were cases 9 and 14, where the findings were borne out by later immunochemical determinations. Case 14 showed in addition, a consistently low level of globulin throughout, as seen by the unusually high A/G ratio of 2.45:1. The data in case 4 showed an elevated level of β-globulin, which may be of interest in view of the report of Cann and Loveless that the β-globulins are chiefly responsible for reaginic activity[3].

In the pre-treatment sera, immunochemical determinations revealed low gamma globulin levels in cases 1, 5, 9, and 14. The normal range by this method being 10 to 12 mg. per ml. of serum.

Analyses of post-treatment sera reveal interesting but inexplicable results. In almost every instance there was an elevation in β globulin levels. The fact that the pooled gamma globulin used in treatment was of a high degree of purity makes this rise in β globulin difficult to explain, and is deserving of further investigation. An elevation in post-treatment gamma globulin levels occurred in cases 3, 4, 5, 7, 9, and 14. One might expect this to occur when the dose of gamma globulin is large enough since the half-life of I_{131}-labeled gamma globulin is reported to be 20.3 days in children (Dixon *et al.*[5]). A lower post-treatment level was obtained in cases 8, 12, and 13, where pre-treatment levels were normal or elevated.

Discussion. The rationale of therapeutic gamma globulin is given considerable impetus by the extensive observations on low resistance to infection associated with abnormalities in the gamma globulin fraction of the blood (Gitlin[8]). Since almost all antibodies reside in this fraction, patients with deficiency or absence of gamma globulin, due either to failure in synthesis, or excessive loss, suffer from recurrent bacterial infection. In such

°We are indebted to Dr. Morris Goodman for carrying out these determinations.

cases, it has been observed that pooled gamma globulin administered in doses of 0.6 to 1.0 ml. per kg. of body weight at monthly intervals affords significant protection. It is also interesting to note that patients with agammaglobulinemia exhibit normal resistance to viral infection. Normal takes with vaccinia virus occur, although antibodies against the virus are either undetectable or of very low titer. However, it is known that very little antibody is required for immunity to certain viruses, as exemplified by the relatively small doses of prophylactic gamma globulin that are apparently successful in pas-

TABLE 3.—GAMMA GLOBULIN STUDY. RELATIVE CONCENTRATION OF SERUM COMPONENTS BY PAPER ELECTROPHORESIS

Patient No. Initials	*% Albumin*		*% α1 Globulin*		*% α2 Globulin*		*% β Globulin*		*% γ Globulin*		*A/G Ratio*	
	Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*
2. D.S.	60	—	3.5	—	11.6	—	11.7	—	11.8	—	1.55	—
3. J.B.	56	—	4.9	—	8.5	—	13.5	—	17.8	—	1.28	—
4. C.G.	54.6	47.7	2.7	3.4	8.1	6.3	18.7	24.3	15.6	18.3	1.21	0.91
5. B.M.	—	60.6	—	4.5	—	8.5	—	13.8	—	12.6	—	1.54
6. J.O.	—	60	—	3.9	—	7.9	—	12.6	—	17.0	—	1.47
7. R.G.	—	50	—	3.7	—	11.0	—	12.6	—	23.2	—	1.0
8. G.K.	57.8	—	3.7	—	—	8.8	12.8	—	17.0		1.36	—
9. G.B.	65.8	51.3	2.6	2.5	8.8	10.0	13.3	17.5	9.7	18.8	1.9	1.05
13. M.M.	62	55.1	3.6	2.9	11.8	12.5	9.1	11.4	13.6	18	1.6	1.23
14. R.S.	71	60.3	2.6	4.3	9.8	10.3	7.1	11.6	9.6	13.8	2.45	1.52

TABLE 4.—GAMMA GLOBULIN STUDY. SERUM GAMMA GLOBULIN LEVELS BEFORE AND AFTER POOLED GAMMA GLOBULIN ADMINISTRATION

Patient No. Initials	*Gamma Globulin Level before treatment mg./ml. of serum*	*Gamma Globulin Level After treatment mg./ml. of serum*	*Clinical Improvement*
1. D.M.	6.9	——	Good
2. D.S.	10.2	10.0	Good
3. M.B.	12.70	13.4	Good
4. C.G.	10.20	13.7	Questionable
5. B.M.	6.20	7.70	Good
6. J.O.	——	9.10	Good
7. R.G.	10.8	12.10	Moderate
8. G.K.	11.50	9.50	Questionable
9. G.B.	8.05	10.9	Good
12. S.S.	16.30	13.10	Questionable
13. M.M.	15.30	9.70	Poor
14. R.S.	8.70	9.30	Moderate

sive protection against measles and infectious hepatitis. There is also experimental evidence that the common cold virus may be neutralized by incubation with pooled gamma globulin (Jackson, Dowling and Anderson[10]).

While it appears reasonable that therapeutic gamma globulin administration should prove beneficial where a lack of this antibody containing fraction exists, asthma is generally not a clinical feature in patients with agammaglobulinemia. In several studies of serum proteins in asthma, an elevation rather than a depression in the gamma globulin fraction of the blood has been shown, with a tendency to be reduced toward normal when clinical improvement occurs (Cooke *et al.*[4], Tuft[14]). Abnormally elevated levels were observed in 2 patients in the current study with a lower reading after treatment. No definite improvement was recorded in either of these cases.

Although the overall results in the present series are not striking, there is indication that the prophylactic administration of pooled gamma globulin is of definite value in certain cases. The data suggest that results may be better in these with some diminution in gamma globulin levels before treatment. Even in patients with normal levels, pooled gamma globulin should be helpful in increasing resistance to certain viral infections. Certainly its use as a therapeutic measure in asthma associated with infection is worthy of further exploration.

Summary. 1. Observations were made on the prophylactic administration of pooled gamma globulin to 15 children, ages 3 to 11, with so-called "infectious asthma." The periods of treatment extended from 8 to 14 months. 2. Dosage of gamma globulin for the most part was from 0.3 to 0.5 ml. per kg. of body weight administered every 3 weeks. 3. Some reduction in the frequency of upper respiratory infections and subsequent episodes of asthma was noted in 8 patients during the periods of treatment. Absence of definite improvement was recorded in the remaining 7 patients. 4. Examination of pre-treatment sera by paper electrophoresis was within normal limits in all but 2 cases. Immunochemical studies of these sera before treatment revealed low levels of gamma globulin in 4 cases, and high levels in 2 others. 5. Post-treatment sera showed elevation in β-globulin fractions in almost all instances. Levels of gamma globulin were increased in 6 cases and diminished in 3 cases following treatment. 6. There is a suggestion from the present study that the results of prophylactic administration of pooled gamma globulin in such asthmatic children may be more favorable where a diminution in serum gamma globulin level exists before treatment.

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SUMMARIO IN INTERLINGUA

Globulina Gamma In Le Tractamento de Asthma Associate con Infection

1. Observationes esseva facite super le administration prophylactic de globulina gamma collectanee in 15 patientes pediatric de etates de inter 3 e 11 annos, omnes suffrente del si-appellate "asthma infectiose." Le periodos de tractamento durava inter 8 e 14 menses. 2. In general, le dosage del globulina gamma esseva inter 0,3 e 0,5 mg per kg de peso corporee administrate a intervallos de 3 septimanas. 3. Un certe grado de reduction in le frequentia de infectiones supero-respiratori e del subsequente episodios de asthma esseva notate in 8 patientes durante le periodo de tractamento. Le absentia de definite provas de melioration esseva constatate in le remanente 7 patientes. 4. Examines pre-tractamental del seros per electrophorese a papiro monstrava valores normal in omne le casos con 2 exceptiones. Studios immunochimic de ille seros ante le tractamento revelava basse nivellos de globulina gamma in 4 casos e alte nivellos in 2 altere casos. 5. Le examine post-tractamental del seros monstrava elevation del fractiones de globulina beta in quasi omne le casos del serie. Le nivellos de globulina gamma esseva augmentate in 6 casos e reducite in 3 secundo examines effectuate post le fin del tractamento. 6. Le presente studio pare indicar que le resultatos del administration prophylactic de globulina gamma collectanee in juveniles con asthma infectiose es possibilemente plus favorabile in casos in que un diminution del nivellos seral de globulina gamma existeva ante le tractamento.

THE INTRAVENOUS GLUCOSE TOLERANCE TEST*

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Recently much attention has been focused on the intravenous glucose tolerance test particularly because the vagaries of glucose absorption make interpretation of oral tests difficult. The disadvantages of the oral tests have been well summarized by Amatuzio, Rames and Nesbitt[1], and by Unger[18]. However, there is lack of agreement as to the method by which intravenous glucose tolerance is most appropriately measured. In general, the method in greatest favor is a method in which a dose of glucose of the order of 25 gm. is administered rapidly and the rate of fall of the blood glucose excess or increment (absolute blood glucose minus the blood glucose before injection) is measured by doing serial determinations of the blood glucose after the injection during a period of approximately one hour. The efficacy of this technique was supported by the observations of Greville[9], of Amatuzio *et al.*[2], and of Duncan[6]. Recent editorials[7,8] called attention to the applicability of this approach and reviewed the reasons the technique in which the increment values were analyzed might be preferable to the technique in which the absolute values of the blood glucose are used. On the other hand, the applicability of the increment blood glucose was questioned by Ikkos and Luft[11] who believe that under certain conditions the most appropriate method of analysis is one of the type employed by Conard and his associates[5] in which the absolute glucose values are used.

The purpose of this paper is to call attention to certain factors which influence the rate of fall of the blood glucose after a glucose load is administered rapidly intravenously. Our observations were designed to yield further information concerning which particular techniques are most appropriate in testing glucose tolerance.

Methods. The observations to be made are based on analyses of certain of our own experimental data and upon our analyses of the data of others, particularly those of Amatuzio *et al.*[2], of Duncan[6], of Silverstone *et al.*[16], and of Ikkos and Luft[11]. The venous glucose levels of our subjects were determined by the method of Nelson[14]. The glucose levels of subjects of the other authors whose data are to be discussed were determined in a variety of ways, but it does not seem likely that these differences accounted for any significant differences in the configuration of the glucose tolerance curves of their subjects.

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The concentration of the glucose injected by these authors was slightly variable as was the manner in which the tests were timed, but all authors injected the glucose in less than 4 minutes and began observations with zero time set at the beginning of the injection or within 4 minutes after the end of the injection. In the discussion which is to follow, differences in the techniques employed are sometimes alluded to because of the possibility that those small variations affected results significantly. However, for the most part, these differences in technique were insignificant.

The methods used in analyzing the several different groups of data are in some instances described in the text of this paper. However, in most instances the details of these analyses are included in the appendix.

to 4 minutes. Our results together with those of other authors are summarized in Table 1.

Apparently, renal excretion in normal subjects averages about 1 gm. after a rapid injection of 25 gm. of glucose. Since this represents only 4% of the administered dose, the effect of renal excretion on the rate at which the load disappears has been considered unimportant (Amatuzio *et al.*[2], Duncan[6], Ikkos and Luft[11]). It should be pointed out, however, that this excretion does not occur at a uniform rate, and that in normal subjects ex-

TABLE 1.—GLYCOSURIA AFTER INTRAVENOUS GLUCOSE IN NORMAL SUBJECTS

Author	*Glucose load in gm.*	*Number of subjects*	*Glycosuria in gm.*
Ikkos and Luft[11]	25	44	Mean of 1.0
Amatuzio *et al.*[2]	25	not specified	0.2 –1.0
Macho[12]	25	22	0.23–1.89
Tunbridge and Allibone[17]	27.6	12	1.4 –2.3
West and Wood (see text)	25	9	Mean of 0.98

All authors administered the glucose rapidly in less than 5 minutes.

Results and Discussion. THE EFFECT OF RENAL EXCRETION OF GLUCOSE ON THE DISAPPEARANCE RATE OF BLOOD GLUCOSE. It is commonly observed that after a load of 25 gm. of glucose is administered rapidly to normal subjects of average size, small amounts of glucose appear in the urine. This is not surprising since the concentration of blood glucose achieved initially is well above the usual renal threshold. For example, in the first 40 normal subjects tested by Amatuzio *et al.*[2] the concentration of glucose in capillary blood averaged 274 mg. per 100 ml. We studied the amount of glucose which appeared in the urine voided by 9 young nondiabetic adults 30 minutes after the start of an injection of 25 gm. of glucose intravenously in 2

cretion would be confined to the first 15 to 25 minutes after a glucose load of 25 gm., since the blood glucose falls below the renal threshold after that time. It has not been possible to determine precisely the effect of renal excretion on the initial portion of the disappearance curve. Nevertheless, it is possible to estimate the magnitude of such effects at various intervals after a rapid injection in the manner described (Appendix A). In the 9 aforementioned young adults in whom we estimated renal excretion, we calculated that 8.4% of the glucose which disappeared was accounted for in the urine during the time the blood glucose levels were above renal threshold levels. In certain of Silverstone's subjects, our theoretical calculations sug-

gested that 12.3% of glucose which disappeared was accounted for in the urine while blood glucose values were above the renal threshold (Appendix A).

It seems likely then, that the renal excretion of glucose produces a small but significant effect on that part of the curve formed by blood glucose values above the renal threshold for glucose. Furthermore, it would appear that when attempts are made to measure glucose tolerance after loads of uniform size which elevate the blood glucose above the renal threshold, the amount of renal excretion and, therefore, to some extent the disappearance rate of administered glucose would depend on three factors which are not related to glucose utilization. These factors are the size of the individual, the renal threshold, and the height of the blood glucose before the start of the test. Large individuals would exhibit less glycosuria because the degree of elevation of the blood glucose produced would be less in proportion to the dosage administered. On the other hand, smaller individuals would exhibit more marked glycosuria because glucose loads of comparable size would produce greater initial levels of blood glucose.

In 17 older subjects ranging in age from 42 to 78, whose fasting blood glucose values were all less than 100 mg. per 100 ml., the amount of glucose which appeared in the urine 30 minutes after the start of a rapid injection of 25 gm. of glucose averaged only 0.6 gm. This suggests that older subjects excrete lesser amounts of glucose after this dose of glucose because of higher renal thresholds for glucose. However, the possibility that incomplete voiding might have been responsible for the lower values in our older subjects could not be excluded. They were ambulatory psychotic patients who had been observing normal diets.

Subjects who have elevated fasting blood glucose values exhibit greater glycosuria because their blood glucose levels immediately after the load are higher initially and remain above the renal threshold for longer periods. The increased glycosuria which results is usually more than counter-balanced by the poor utilization, and, therefore, the apparent rate of utilization as measured by the disappearance rate of blood glucose is usually abnormally low (Amatuzio *et al.*[2]). However, occasionally glycosuria is so intense that a falsely normal glucose tolerance results (Appendix B).

THE EFFECT OF EXTRACELLULAR EQUILIBRATION ON GLUCOSE DISAPPEARANCE. Raisz, Young, and Stinson[15] found that in dogs apparently complete equilibration of rapidly injected sucrose occurred in some instances as early as 10 minutes and usually within 20 minutes after the injection. However, White and Rolf[19] administered sucrose rapidly to 3 nephrectomized dogs and found that under the conditions of their experiment 1.5 to 2 hours were required before apparent equilibration occurred. On the basis of data available at present, it would not be possible to be certain concerning the rate at which equilibration occurs in man after a rapid injection of sucrose.

Furthermore, it is quite possible that extracellular mixing would occur more rapidly with glucose than with sucrose since the glucose molecule is smaller. In the normal subjects of Ikkos and Luft, the rate of fall of the blood glucose slowed at about 25 minutes after the rapid injection of 25 gm. of glucose. They hypothesized that this change was due to the fact that up to this point a certain percentage of the rate of disappearance was attributable to the process of extracellular mixing. It is of interest, however, that the mean capillary blood glucose of these subjects at this time was 177 mg.

per 100 ml. This introduces the possibility that the change in rate to some extent was due to the fact that significant glycosuria was occurring during the earlier period (see above). It seems likely that both glycosuria and the process of extracellular equilibration contribute to the greater disappearance rate which is observed under these conditions during the initial part of the glucose tolerance curve.

It is not possible at present, then, to be certain of the precise degree to which the process of equilibration of glucose contributes to its disappearance rate at any given time. However, inspection of the data of Conard reveals that the rate of glucose disappearance had become constant 15 minutes after an injection at a time the mean blood glucose was 170 mg. per 100 ml. This would seem to suggest

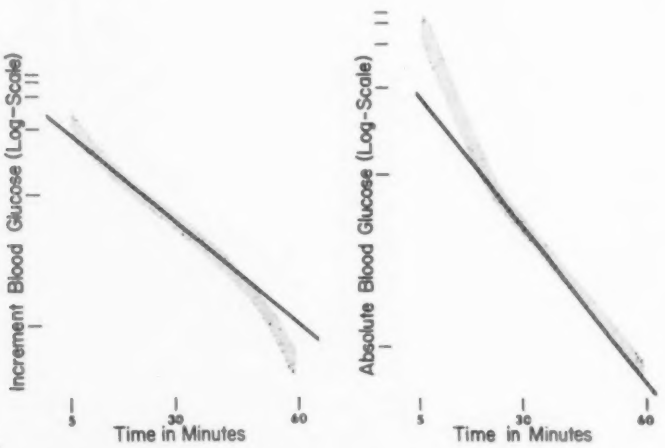

Fig. 1.—Schematic representation of the configuration of the tolerance curve in normal subjects after the rapid injection of 25 gm. of glucose when increment (glucose excess) values are plotted (on the left), and when absolute blood glucose values are plotted (on the right). The lines formed by the shaded area represent the areas into which typical glucose tolerance curves fall. A black line which is straight is superimposed on each curve for comparison. These curves were drawn in order to summarize roughly the findings of several authors each of which used slightly different techniques. The analyses on which these graphs are based are explained in the text.

It should be mentioned that if both utilization and equilibration were occurring at rates which were approximately exponential in regard to time, the log plots of the resultant serial blood glucose values would yield an approximately straight line. Therefore, the fact that the plots form a line which is approximately straight does not necessarily rule out the possibility that equilibration is still in the process of occurring.

that either extracellular mixing was virtually complete within 15 minutes, or that other kinetic factors such as continuing equilibration and increasing glucose release from the liver were producing effects, as the blood glucose was falling toward normal fasting levels, which approximately balanced each other. The latter explanation seems most likely.

It is, of course, quite possible that the rate and duration of the equilibra-

tion process may vary with the size of the dose. It also seems likely that marked changes in the size of the extracellular space would result in changes in the rate at which glucose would disappear initially. On the other hand, in subjects with glucose spaces of normal size, the effect of the process of equilibration on the rate of disappearance of glucose would probably be constant from individual to individual if the dose of glucose were varied according to body size (see below).

THE DISAPPEARANCE CURVE OF THE INCREMENT BLOOD GLUCOSE. It was shown by Amatuzio *et al.*[2], and by Duncan[6] that when 25 gm. of glucose were administered rapidly intravenously to normal subjects the levels of the blood glucose increment (or excess) when plotted on a log scale fell in a relatively straight line until the blood glucose began to approach the pre-injection level (see Fig. 1). However, inspection of certain of the data of Amatuzio reveals that the disappearance rate when calculated in this way begins to increase when blood glucose values are still well above the pre-injection level and that the straight line relationship between the log of the increment blood glucose and time did not exist when levels of blood glucose increment were below 48 mg. per 100 ml. (Appendix C).

The observations in part C of the Appendix also indicate that although the rate of fall of the glucose increment in normal subjects after a rapidly injected load of 25 gm. is approximately constant over a one hour period, it may not be precisely constant for more than a few minutes at any one time, being slightly more rapid initially than in the middle part of the curve, and being increasingly more rapid in the latter part of the curve after the increment blood glucose has fallen to levels below 40 to 50 mg. per 100 ml.

In view of the observations above concerning the effect of urinary excretion and the process of equilibration on the glucose disappearance rate during the early part of the curve, it seems likely that the slightly more rapid disappearance of the increment which obtains initially could be explained by these phenomena. Indeed, if urinary excretion and equilibration were not occurring, the rate at which the increment disappeared initially after 25 gm. of glucose would undoubtedly be substantially slower than the rate of fall during the middle part of the curve. That this is so is indicated by the results of our analysis of the data of Conard (Appendix D).

Our impressions concerning the configuration of the curve representing disappearance of the glucose increment in normal subjects are summarized schematically in Fig. 1.

THE DISAPPEARANCE CURVE OF THE ABSOLUTE BLOOD GLUCOSE. When glucose loads of 25 gm. were administered intravenously rapidly to normal subjects and the blood glucose levels determined repeatedly for one hour after the injection, the rate of fall expressed as a per cent per unit of time remained approximately constant during that period (Silverstone *et al.*[16]). However, as has been indicated above, the rate of disappearance is more rapid initially. For example, in 24 of our subjects whose fasting blood glucose values averaged 75 mg. per 100 ml., we found that the mean absolute blood glucose fell 26.9% during the period 10 to 25 minutes after the start of a rapid intravenous injection (50 mg. of 50% glucose in 2 to 4 minutes), while it fell only 20.5% during the period 25 to 40 minutes after the injection. The reasons for these differences in the rates of disappearance have been discussed above. The absolute blood glucose levels of the subjects of other investigators (Amatuzio *et al.*[2], Dun-

can[6], Ikkos and Luft[11], Silverstone *et al.*[16]), who administered 25 gm. of glucose rapidly intravenously also fell more rapidly during the first 20 to 30 minutes after the injection than during the succeeding period.

In normal subjects of Ikkos, and in those of Amatuzio, the rates of fall of the blood glucose when expressed as percentage fall per unit of time were constant during the second 30 minutes of the observations at the end of which time the mean blood glucose levels were 34 mg. per 100 ml. and 19 mg. per 100 ml. respectively, above pre-injection levels. However, in analyzing preliminary data of our own and data of others (Conard *et al.*[5], Duncan[6], Silverstone *et al.*[16]), we note a very slight tendency which may or may not be significant for the rate of fall to decrease during the latter part of the curve before pre-injection levels have been reached. It is quite possible that minimal slowing of the rate of fall of blood glucose as it approaches normal fasting levels could be due to the fact that the glucose output of the liver begins to increase to some extent at this point. This opinion is based on speculation since we have not studied the glucose output of the liver under these circumstances. However, the data of Bondy *et al.*[3], and of Cahill *et al.*[4] suggest the possibility that after the blood glucose has been elevated, the glucose output of the liver may resume to some extent before the blood glucose values have returned to normal.

In summary, the absolute blood glucose level falls at a rate which is approximately exponential in regard to time. However, for the reasons outlined above, the rate of fall is slightly more rapid initially than during a later period, when glucose loads of 25 gm. are administered to subjects whose fasting blood glucose values are normal. The rate of fall expressed as per cent fall per unit of time, becomes constant about 20 to 30 minutes after the injection and remains so for the next 30 to 40 minutes. It is possible that the rate of disappearance slows very slightly in the last few minutes of the first hour even in subjects whose blood glucose levels are above pre-injection levels, but the rate of fall is virtually constant during this second half hour. The configuration of the disappearance curve of the absolute glucose in normal subjects is schematically represented in Fig. 1.

COMPARISON OF THE APPLICABILITY OF ABSOLUTE AND OF INCREMENT GLUCOSE VALUES IN MEASURING GLUCOSE TOLERANCE. Amatuzio, Rames and Nesbitt[1], recommended the use of increment values in calculating intravenous glucose tolerance because under the circumstances of their observations they found that analysis of increment values yielded more constant results than did analysis of absolute values. Duncan[6] was of the same opinion and showed that under the circumstances of the analysis he carried out the use of increment values yielded more reproducible results when duplicate tests were done with identical glucose loads and also when they were done with glucose loads of differing sizes. On the basis of these observations, this particular method has gained wide acceptance (Editorial[7], Forsham[8]).

On the other hand, Ikkos and Luft have pointed out certain advantages of using absolute values, particularly stressing the fact that there are marked differences in the rates of disappearance of the increment glucose during the latter part of the curve as compared to the earlier parts. This point has been discussed above. We regard this as an important criticism of this method particularly because it means that it would be less effective in de-

termining glucose tolerance at what might be called physiological levels of hyperglycemia. Since the hyperglycemia which occurs in normal individuals after a meal is of the order of 30 to 70 mg. per 100 ml., it would seem to be of importance to be able to evaluate the rate of fall while blood glucose values were falling from these levels toward fasting levels.

Certain observations described in the earlier portion of this paper indicate that, when the glucose increment values obtained after the effects of renal excretion and extracellular equilibration have ceased or diminished are plotted logarithmically against time, a line is formed which is convex (see Fig. 1). During the initial portion of the curve, certain factors not related to glucose utilization produce a counter-distortion of the line which tends to straighten this upper part of the line. On the other hand, when absolute values are plotted the distortions produced by the glycosuria and extracellular equilibration are unopposed and, therefore, the upper part of the line is less straight than when increment values are plotted. It is, therefore, possible that the greater variability of results when absolute values are used, was to some extent due to the fact that the upper segments of the lines formed by the plots of these values were more curved than the lines formed by the plots of the increment values.

In Duncan's subjects who were studied after both 25 and 50 gm. of glucose, we found that the rates of fall of the absolute glucose values during the first 20 minutes were approximately twice as great as during the last 20 minutes of the hour after each of the 2 loads. On the other hand, at points on each of the 2 curves (after 25 and 50 gm. of glucose) when blood glucose levels were comparable, disappearance rates were comparable (Appendix E).

Under the conditions of his analysis, Duncan[6] observed that the rate of fall of the increment remained unchanged with the 50 gm. dose as compared to the 25 gm. dose. On the other hand, we found that in his subjects rates of fall of the increment were similar after the 2 different loads only during the first 40 minutes of the test (Appendix F). Furthermore, when the latter parts of the curves were compared, the rate of glucose disappearance was less variable with differing doses of glucose when the values of the *absolute* glucose values were used than when increment values were used (Appendix F).

It is possible that the differences in the initial rates of disappearance of the absolute glucose which occur when the size of the glucose load is varied are due to factors which are unrelated to glucose utilization such as differences in the intensity and duration of renal excretion and differences in rates and duration of extracellular equilibration.

That the constancies or inconstancies of the rates of fall of the increment or the absolute glucose may be better related to the levels of the blood glucose than to time or to the amount of glucose administered, *per se,* is supported by the following observation. When insulin was administered intravenously with glucose the rate of fall of the absolute glucose remained constant during the period 10 to 25 minutes after the injection while the blood glucose was falling from 179 mg. to 77 mg. per 100 ml. On the other hand, the rate of fall of the increment glucose changed markedly during this period (Appendix G).

Duncan suggested the possibility that the change in the rate of disappearance of the increment which occurs as the increment values approach zero might be due to the "intervention of adaptive processes." This seems unlikely for the following reasons. First of all, at this stage, it would seem

more reasonable for "adaptive processes" to result in a slowing of the disappearance rate rather than in an acceleration. Secondly, if it is to be assumed that the adaptive process is a result of a stimulus which is related to the level of the increment glucose, *per se*, then it must be assumed that some sort of physiologic receptors exist which are responsive to the level of the glucose increment but not to the actual level of the blood glucose (since the disappearance rate of the absolute blood glucose remains relatively unchanged during the period when the blood glucose is approaching normal fasting levels). The marked acceleration in the rate at which the glucose increment disappears at this stage suggests to us that this technique of analysis has no applicability to what is transpiring physiologically at this time.

The intra-individual difference between duplicate tests when absolute values and when increment values are used. By analyzing his own data and that of Amatuzio *et al.*[2], Duncan found that when duplicate intravenous glucose tolerance tests were done using a dose of 25 gm. in each series of individuals, the intra-individual variations of the results were greater when the rate of fall of the absolute glucose level was determined than when the rate of fall of the increment was examined. However, the observations recorded in the appendix under the letter "H" suggest that this difference is apparent only, and that it is probably related to the techniques of analysis employed.

Our observations, then, lend no support to the opinion that there are advantages to be gained by analyzing the rate at which the blood glucose increment (or excess) disappears. Indeed, if glucose tolerance is to be evaluated by calculating a rate constant, it would appear to be more appropriate to analyze the absolute values (at a time when the rate of disappearance is most closely related to glucose utilization).

SOME THEORETICAL CONSIDERATIONS IN EVALUATING METHODS OF TESTING GLUCOSE TOLERANCE. The practical efficacy in establishing the presence or absence of diabetes of techniques which employ the analysis of either the absolute blood glucose values or the increment values cannot be easily established. This is true of any test designed to indicate the presence or absence of diabetes of minimal severity since it is necessary to try to establish its efficacy by comparing the responses of individuals to the new test with their responses to another test or tests which one is trying to improve upon. For example, Amatuzio *et al.*[2], have shown that by calculating the disappearance rate of the blood glucose increment they could very satisfactorily separate "diabetics" from "nondiabetics." It should be noted, however, that the presence of diabetes must have been established or excluded on the basis of certain other tests which were, theoretically, less reliable. It might be reasonably argued that this shows that the older tests are equally satisfactory since the results correlate very well with the results from the new test.

For these reasons, in evaluating the efficacy of a test for very mild diabetes, one has to depend to some extent on theoretical considerations. One has to decide the size of glucose load which is theoretically most appropriate, what portion of the disappearance curve should be studied, how rapidly the glucose should be administered, how the results should be analyzed, and so forth. The most appropriate test of glucose tolerance should be one which measured the rate at which glucose disappeared, but which was not affected appreciably by factors which are not related to the presence or ab-

sence of diabetes such as the renal threshold for glucose and variations in body size. On the basis of some of the observations above, it would seem reasonable to recommend that in trying to evaluate glucose tolerance the rate of fall of the blood glucose be studied from the time values are just below renal threshold levels until fasting levels are reached or approached.

A test which relies on the calculation of a rate constant from a line formed by the plots of several values may have 2 disadvantages. First of all, multiple sampling and multiple determinations are necessary and secondly, attempting to draw a line through plots which under certain conditions actually form a slightly convex or concave line would provide an additional possible source of error. Although certain criticisms have been made of such methods, it should be emphasized that under certain conditions they probably measure glucose tolerance with considerable precision, and they have the advantage of not having to rely entirely on one or 2 blood glucose determinations.

It should be mentioned that the rates of fall of the venous blood glucose and the capillary blood glucose may not be precisely the same at any one time. However, we have not been able to identify significant differences between the configuration of the glucose tolerance curves when capillary blood glucose determinations were used (Amatuzio *et al.*[2], Duncan[6], Ikkos and Luft[11]) and those curves based on venous blood glucose determinations (Conard *et al.*[5], Silverstone *et al.*[16]). Holten, Lundbaek and Staffeldt[10] were unable to find any differences in the configurations of glucose tolerance curves when serial determinations of the venous and of the capillary blood glucose were determined simultaneously in 17 subjects after rapid intravenous administration of 25 gm. of glucose. In the subjects of Mosenthal and Barry[13] to whom glucose was administered orally, the mean differences between the capillary and the venous blood glucose were 25 mg. per 100 ml. at 30 minutes when the mean capillary blood glucose was 156 mg. per 100 ml. and 30 mg. per 100 ml. at 2 hours when the mean capillary blood glucose was 113 mg. per 100 ml. The very slight difference in the percentages of fall of the capillary and venous glucose levels which occurred under these conditions may or may not be significant.

SIMPLIFIED GLUCOSE TOLERANCE TESTS. As a result of certain of the observations above, we concluded that glucose tolerance could be easily estimated with considerable accuracy by determining the rate of fall of the blood glucose during a period of approximately 30 minutes at a time when the levels of blood glucose are a little below the renal threshold, but above the normal fasting level. Since the per cent per minute fall is constant during this period, it seems likely that glucose could be estimated accurately by performing only two blood glucose determinations. The rate of fall could be expressed as per cent fall in 30 minutes or as per cent of the initial level remaining in 30 minutes.

Amatuzio *et al.* have already evaluated the degree to which single blood glucose values at certain intervals of time after a rapid injection of glucose might serve as an index of the rate of fall during the preceding period. They found that after 25 gm. of glucose had been injected, the blood glucose 68 minutes later was a fairly satisfactory index of glucose tolerance. It seems logical to assume that if the size of the glucose load was varied in each subject according to the size of the glucose space, a blood glucose determination about 40 to 60 minutes after

injection would be an excellent index of glucose tolerance. We are evaluating the validity of this hypothesis.

We have examined the correlation between the venous blood glucose at 40 minutes after the start of an injection, and the per cent of fall during the 30-minute period ending at 40 minutes in 15 apparently nondiabetic subjects to whom 0.1 gm. of glucose per pound of body weight was administered in 1 to 2 minutes. The negative correlation coefficient was excellent ($r = -0.91$). This suggests that under these conditions, the 40-minute value itself to a large degree reflected the rate at which glucose had disappeared.

A test of this type employing a single blood glucose determination at 40 minutes would have the advantage of requiring a smaller injection of glucose, and of not being significantly affected by renal excretion of glucose. It would be less influenced by interindividual variations in the size of the glucose space than are tests in which the dosage of glucose is not varied according to the size of the subject. A fasting blood glucose determination would not be required. This method would have the disadvantage of being completely dependent on the accuracy of one glucose determination. Furthermore, it could be assumed that interindividual variations in the relative size of the extracellular fluid compartment such as might occur in edematous subjects would also influence the rate of disappearance to some extent, but in subjects with normal extracellular spaces, this factor would be approximately constant.

Since the size of the glucose space is probably more closely related to lean body mass than to actual body weight, it may be assumed that an ideal test of this type would include adjustment of dosage of glucose on the basis of lean body mass. Nevertheless, it seems likely that using dosages based on actual weight would probably be satisfactory in individuals who were not exceedingly obese or exceedingly thin. Perhaps, the so-called ideal body weight or the so-called body surface area would be a little better correlated with the size of the glucose space than is actual body weight. Since many of the subjects who are tested for diabetes are obese, the relationship between obesity and the size of the glucose space will need to be determined before results of tests employing single determinations of the blood glucose can be evaluated completely in obese subjects.

In order to determine the intraindividual variation of the blood glucose 50 minutes after intravenous glucose (25 gm.) we analyzed the data of Duncan in the 19 subjects, mentioned in part "H" of the Appendix, who had duplicate tests. It was found that the correlation coefficient was excellent ($r = 0.90$) indicating that these values were quite reproducible from day to day in the same subject.

Summary and Conclusions. When a glucose load of a standard size is administered rapidly intravenously, the rate of fall of the blood glucose during the first 25 minutes after the injection may be influenced by several factors which are not related to the rate of glucose utilization. Some of these factors are the size of the glucose space (which is in turn related to body size), the height of the blood glucose before the injection, the renal excretion for glucose, and the size of the glucose load.

In normal subjects, the rate of disappearance of the blood glucose after a rapidly administered glucose load of 25 gm. usually remains exponential in regard to time during the period 25 to 60 minutes after the injection at a time when the blood glucose is falling from

levels near the renal threshold for glucose to levels at or just above preinjection levels. It seems likely that during this period the rate of disappearance of the absolute glucose is well related to glucose utilization although some other factors are probably operative. On the other hand, during this same period the rate of disappearance of the increment blood glucose (or glucose excess) is inconstant in that the log plots of these values against time form a convex rather than a straight line. Evidence is presented which suggests that the advantages of analyzing increment rather than absolute values which have been described previously were apparent rather than real.

Glucose tolerance can be measured by administering a load rapidly intravenously of sufficient size to produce the hyperglycemia of a "physiologic" magnitude and by determining the rate of fall from a time the blood glucose is near the renal threshold for glucose until it is approaching the preinjection level. Evidence is presented suggesting that under certain conditions, fairly accurate estimation of glucose tolerance may require only one or 2 determinations of blood glucose.

APPENDIX. A. The weights of these 9 subjects averaged 65.5 kg., and the mean venous blood glucose values 10 minutes and 25 minutes following the start of the rapid injection of 25 gm. of glucose, were 234 and 165 mg. per 100 ml., respectively. Before the injection, the mean blood glucose was 82 mg. per 100 ml. If one assumes that the administered glucose was distributed in a volume equivalent to 22% of the body weight (Silverstone *et al.*[16]) and that virtually all glycosuria occurred at a time when the mean blood glucose level exceeded 175 mg. per 100 ml., then one could calculate that the increment of the injected glucose remaining (93 mg. per 100 ml.) represented 13.4 gm. of glucose at the time the renal threshold was reached. Thus, at the time levels of 175 mg. per 100 ml. were reached 11.6 gm. of administered glucose (25 minus 13.4) would have disappeared during a time when 0.98 gm. appeared in the urine. Thus 8.4% of the glucose which disappeared was accounted for in the urine during the time the blood glucose levels were above the renal threshold.

The weights of 12 young adult nondiabetic subjects of Silverstone *et al.*[16], were available so these same theoretical calculations were performed on those data. Glycosuria was not measured, but assuming that it amounted to 1 gm. (4% of the administered dose) then glycosuria would have accounted for a 12.3% of the disappearance of glucose during the time when venous blood glucose levels exceeded 175 mg. per 100 ml.

B. We studied a 66-year-old woman, with a fasting blood glucose level of 215 mg. per 100 ml. who exhibited levels of 450, 382, and 311 mg. per 100 ml. at 10, 25, and 40 minutes respectively, after the start of an injection of glucose of 25 gm. which was completed in 3 minutes. Thus, during a 30-minute period the blood glucose fell 31%. The rate of disappearance was not significantly different from the rates of 14 apparently nondiabetic subjects whose ages matched those of this diabetic subject. Their fasting blood glucose levels were all less than 100 mg. per 100 ml. The mean fall of the blood glucose in these 14 elderly subjects under identical circumstances was 34.8% with standard deviation of 8.4%. The precise amount of glycosuria which occurred during the test was not measured in this diabetic subject, but semi-quantitative testing revealed that the 4 plus glycosuria was occurring before and during the glucose tolerance test. Thus it appears that the marked glycosuria exhibited by this subject accounted for a falsely normal glucose tolerance test.

C. For example, analysis of data from the first 6 of Amatuzio's subjects in which the tests were done in duplicate reveals that in each of 12 instances the rate of fall of the increment during the period 40 to 56 minutes after the peak level was greater than during the period 24 to 40 minutes after the peak. These differences are statistically significant ($p<.001$). The mean blood glucose increments were 76, 48, 21 mg. per 100 ml. at 24, 40, and 56 minutes, respectively.

We also analyzed the rate of fall of the increment in the first 40 of the normal subjects of Amatuzio *et al.*, during the first 16 minutes and during the second 16 minutes of the test. Althoughs there were no significant differences in the rates of fall, the fall of the increment averaged 45% during the earlier period and was slightly less during the following 16 minutes

(42.5). On the other hand, data were analyzed from the tests of each of 8 normal subjects of Duncan's Table 3. It was found that after 25 gm. of rapidly injected glucose the rate of fall of the increment in these subjects was in every instance greater during the first 15 minutes of the observed fall than during the second 15 minutes.

D. Conard *et al.*, administered lesser amounts of glucose (averaging 19.7 gm.) thus producing concentrations of glucose which did not significantly exceed the renal threshold for glucose during the period when the rate of fall was observed. We found that the rate at which the increment of venous blood glucose disappeared in these 20 normal subjects was significantly slower initially during the period 15 to 30 minutes after the intravenous injections than during the following 15 minutes ($p<.05$).

E. We found that in subjects of Duncan after a dose of 25 gm. was administered the fall of the mean absolute blood glucose between 20 and 30 minutes was 14.8% at a time when the mean blood glucose values were falling from 176 to 150 mg. per 100 ml. The fall after 50 gm. of glucose in these subjects was the same (15.4%) during a different 10-minute period (40 to 50 minutes) at a time when the mean blood glucose values were falling from 176 to 149 mg. per 100 ml.

F. Analysis of the data of Duncan shows that 7 of 8 subjects had greater rates of fall of the increment during the 10-minute period starting with the fortieth minute when 25 gm. were administered than when 50 gm. were administered. During the following 10-minute period (50 to 60 minutes) each of the 7 subjects whose blood glucose levels had remained above the pre-injection levels exhibited greater rates of fall after the smaller dose. During this same 10-minute period these 7 subjects had slightly greater rates of fall of the absolute glucose after the larger dose of glucose, but these differences were small since the fall of the blood glucose after the dose of 25 gm. was 12.4%, while after the dose of 50 gm. it was 10.1%.

G. Analysis of the data of Silverstone shows that when 12 young adults were given a rapid intravenous injection of 25 gm. of glucose together with 5 units of insulin per square meter of body surface, the mean absolute glucose fell from 179 mg. per 100 ml. at 10 minutes after the start of the injection to 77 mg. per 100 ml. (8 mg. per 100 ml. above the preinjection level) at 25 minutes. During each 5-minute segment of this 15-minute period the percentage fall of the mean absolute glucose remained relatively constant. The values were 26.9%, 21.4% and 25.3% respectively for each of the 3 periods of 5 minutes. On the other hand, the rate of fall of the mean glucose increment did not remain constant. The mean percentages of fall during each of these 5-minute periods were 43.7, 45.2 and 76.5%, respectively.

H. The rates of fall of the absolute glucose levels in the subjects of Duncan who had duplicate tests were markedly different in the earlier as compared to the later part of the curve. The per minute fall averaged 1.36% as determined by the method he employed in which an attempt is made to draw a straight line through the log plots of the values. However, analysis of these data shows that the mean blood glucose fell 46.2% during the first half hour of the descent while during the second half hour a fall of only 30.0% occurred. Thus the rate of fall in the first half hour was much greater than in the following half hour. It may be assumed that a technique which yields a result based on the slope of a line drawn through these plots which did not form a straight line would be likely to yield answers which would be somewhat variable. This variable can be eliminated by comparing the percentages of fall during one or more arbitrarily selected intervals since this would not require that lines be drawn.

In order to eliminate the effect of renal excretion and to minimize the effect produced by the process of extracellular equilibration, we selected for analysis the blood glucose levels of Duncan's subjects at 20 and 50 minutes at a time when the mean levels of capillary glucose were 186 mg. and 125 mg. per 100 ml., respectively. In order to compare the intraindividual reproducibility of the disappearance rates of the increment blood glucose and of the absolute blood glucose, we compared the variation of the percentages of fall during this half hour period in 19 of these 20 subjects to whom 25 gm. of glucose were administered. One subject was omitted because the pre-injection level of blood glucose had been reached before 50 minutes. The variations between each of the duplicate tests were expressed as percentage variation between the first test and the second test. This was done by dividing the difference between the 2 tests by the value for the first test and then multiplying the result obtained by 100 in order to express the difference as a percentage of the first test. The average intra-individual variation of the increment fall was 3.6% while the average variation of the absolute fall was 6.9%. However, it should be noted that when the results of these same tests were expressed as per cent of the increment and of the absolute values *remaining* then the intra-

individual variation of the tests was greater when the increment values were used (7.7%) than when absolute values were used (3.3%).

The correlation coefficient of the percentage of fall in these duplicate tests was somewhat greater when increment values were analyzed ($r = 0.88$) than when the absolute values were analyzed ($r = 0.71$). However, this difference is not statistically significant and is attributable to the fact that the fasting blood glucose levels were less variable intra-individually than among individuals. A similar increase in the correlation coefficient could be produced by subtracting either the body weight of the individual or the eosinophil count of the individual from each of the absolute blood glucose values. Of course, these latter 2 entities have no relevance, but the examples are given to show that a greater correlation coefficient may be achieved by subtracting from the absolute glucose values any values which are more variable interindividually than intraindividually. Since we question the physiologic relevancy of the glucose increment in this situation (see above) we believe that the slightly greater correlation coefficient achieved with the increment values is probably fortuitous and not relevant.

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SUMMARIO IN INTERLINGUA

Test del Tolerantia pro Glucosa Intravenose

Quando un carga de glucosa de quantitate standard es administrate rapidemente per via intravenose, le rapiditate del reduction del nivello de glucosa in le sanguine durante le prime 25 minutas post le injection es possibilemente influentiate per plure factores non relationate con le mesura del utilisation de glucosa. Iste factores include (1) le dimensiones del spatio de glucosa (le qual, de su parte, es relationate con le dimensiones del corpore), (2) le concentration del glucosa in le sanguine ante le injection, (3) le excretion renal de glucosa, e (4) le magnitude del carga de glucosa.

In subjectos normal, le rapiditate del disparition de glucosa ab le sanguine post le administration rapide de un carga de 25 g remane usualmente exponential con respecto al tempore, durante le periodo de inter 25 e 60 minutas post le injection, a un tempore quando le glucosa del sanguine descende ab nivellos in le vicinitate del limine renal pro glucosa usque a nivellos equal o pauco superior a illos presente ante le injection. Il pare probabile que durante iste periodo le rapiditate del disparition de glucosa absolute es ben correlationate con le utilisation de glucosa, ben que certe altere factores es probabilemente etiam de importantia. Del altere latere, durante iste mesme periodo le rapiditate del disparition del addite glucosa (o del excesso de glucosa) in le sanguine es inconstante, a judicar per le facto que le curva del logarithmos de iste valores como function del tempore es un linea convexe plus tosto que derecte. Es presentate observationes que indica que le avantage, previemente describite, de analysar le valores del glucosa additional plus tosto que le valores absolute de glucosa, es illusori e non real.

Le tolerantia pro glucosa pote esser mesurate per administrar un carga rapidemente per via intravenose, providite que illo es sufficientemente grande pro effectuar un hyperglycemia de magnitude "physiologic," e per determinar alora le rapiditate del reduction del glucosa sanguinee a partir de un tempore ubi su concentration es in le vicinitate del limine renal usque al tempore ubi illo es proxime al valor pre-injectional. Es presentate datos que indica que, sub certe conditiones, satis accurate estimationes del tolerantia pro glucosa pote esser obtenite per medio de solmente un o 2 determinationes del nivello de glucosa in le sanguine.

SUMMARIO IN INTERLINGUA

(See page 1 for original article)

Methimazol e Carbimazol in Hyperthyroidismo: Comparation per Medio de un Technica Double-Blind

1. Methimazol e carbimazol, identificate solmente per numeros de codice de signification non explicate, esseva administrate a 123 patientes in un serie de 203 essayos. Methimazol esseva administrate initialmente a 68 patientes, carbimazol a 55.

2. Le influentia exercite per le un e le altere del duo preparatos es describite con respecto al rapiditate e al completessa del resultante stabilisation, al dosage usate, e al alterationes notate in un varietate de manifestationes clinic.

3. Le duo preparatos, peso per peso, pareva esser equalmente efficace in stabilisar le manifestationes de hyperthyroidismo.

4. Esseva incontrate 8 reaction toxic durante le administration de methimazol, 6 durante le administration de carbimazol. In le caso de methimazol, duo del reactiones esseva urticario-febril. Le altere 12 reactiones esseva characterisate per un o plures del sequente aspectos: prurito, eruptiones localisate, e edema transiente.

5. Es concludite que methimazol si ben como carbimazol es efficace agentes thyroido-blocante de approximativemente le mesme grado de activitate. Il es possibile que methimazol es plus toxic, sed multo multe casos additional debe esser studiate ante que un conclusion definitive pote esser formulate con respecto a iste assertion, proque le differentias notate in le presente studio non es statisticamente significative.

THE FREE ACHILLES REFLEX DURING TREATMENT OF HYPERTHYROIDISM

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and

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In a previous report the free Achilles reflex was studied throughout the spectrum of thyroid function from hyperthyroidism to myxedema (Lawson[5]). Later, the overall diagnostic accuracy of the Achilles reflex test was compared to the conventional tests of thyroid function in over 3000 patients (Lawson[6]).

While the reflex determinations as recorded by our apparatus appear promising in the diagnosis of thyroid dysfunction it has become clear that the prime value of such an endorgan test is in following the effects of therapy once the diagnosis has been established using all the available diagnostic means at hand.

It is the purpose of this report to present the reflex findings which occurred in 44 patients undergoing treatment for hyperthyroidism during an observation period of over 3 years.

Methods and Materials. APPARATUS. The free Achilles reflex was recorded using a new electromagnetic device, the kinemometer, which has been described in a previous publication[5]. The apparatus is very similar to the velocity ballistocardiograph. There are several pertinent differences which should be understood, however. The unit is composed of two identical coils of approximately 100 millihenries inductance. The coils are placed side by side and connected in series. The cores of the coils are L-shaped and oriented in such a manner that the offset portions face away from each other. If a horse shoe magnet is moved near the offset portions of the coil assembly, only the movement directly away from the coil unit will cause a significant current generation. This makes it possible to record movement in only one plane, although the movement may be complex in three planes simultaneously. Practically, this means that although the magnet is taped to a patient's free heel as shown in Fig. 1 and the movement may have components in three planes due to the hammer blow, only the movement of the heel due to gastrocnemius and soleus muscle contraction will be recorded Further, any extraneous electrical field such as 60 cycle AC current will be neutralized by the coils, since they will be "bucking" each other. Extensive shielding is, therefore, unnecessary. Considerable care should be taken to assure equal inductance in the two coils, or vertical and lateral movement artifacts will affect the accuracy of the tracings.

Another problem, which causes some concern to physicians who have used the device, relates to the fact that upon striking the Achilles tendon vibrations are set up in the tendon and associated structures. These vibrations are in the plane of movement and hence are sometimes superimposed on the smooth reflex curve. It is very simple electrically to remove these rapid vibration components by simply attaching a 500 microfarad condenser across the EKG leads. If this is done, the rapid tendon vibrations will be effectively removed, but the S–D interval of the reflex tracing (see Fig. 2) will be lengthened 40 milliseconds. This relates to the condenser charge time and is constant, irrespective of the velocity of movement or total reflex duration. The 500 microfarad condenser was chosen because the 40 millisecond lag induced corresponds to exactly one small square on the standard electrocardiogram and hence the values previously reported for the normal and abnormal contraction (S–D) intervals can still be easily utilized.

Using the kinemometer, the Achilles reflex is recorded as a diphasic curve as shown in

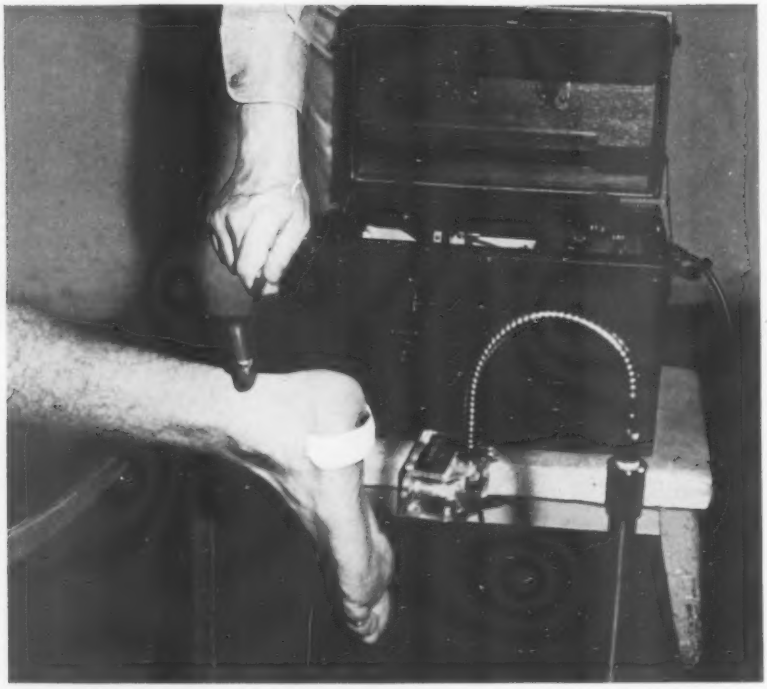

Fig. 1.—Arrangement for clinical recording of the Achilles reflex. Note magnet taped to the patient's heel and standard electrocardiograph.

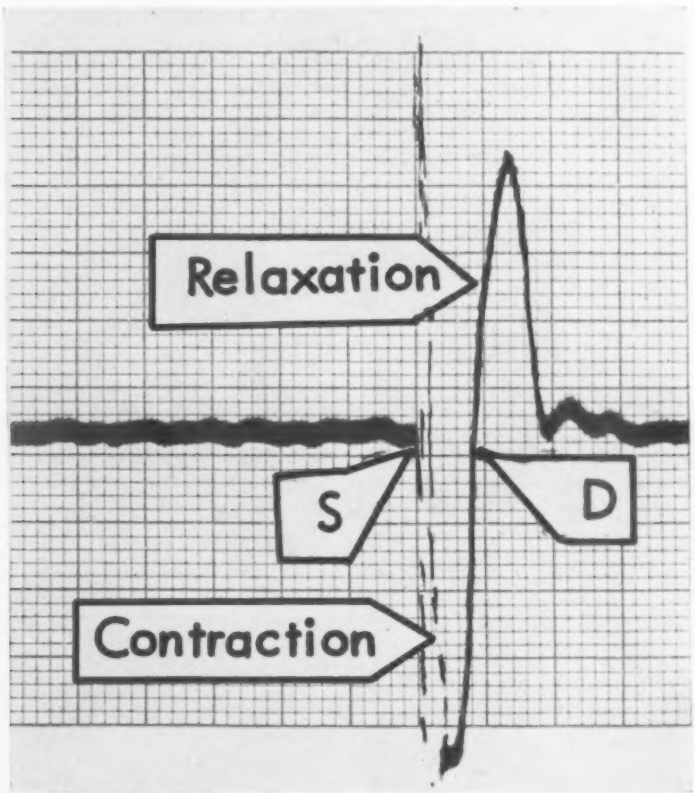

Fig. 2.—The free Achilles reflex as recorded by the kinemometer. Note particularly the S–D interval representing the interval from stimulus to the end of contraction

Fig. 2. With this recording form it is possible to study contraction and relaxation as separate entities with precision. The actual apparatus is shown in Fig. 1. Although the Achilles reflex is usually obtained as shown due to its easy accessibility, it is equally possible to obtain biceps and quadriceps reflexes by placing the magnet on the body of the muscle to be tested. The S–D intervals obtained thereby are the same as with the Achilles reflex.

cle contraction time is concerned, are presented in Fig. 3. The similar results of treatment with preoperative thiourea compounds and surgery are presented in Fig. 4. The 4 patients treated with propylthiouracil alone differed in no significant manner from the other cases shown graphically. Several interesting points can be noted in both graphs:

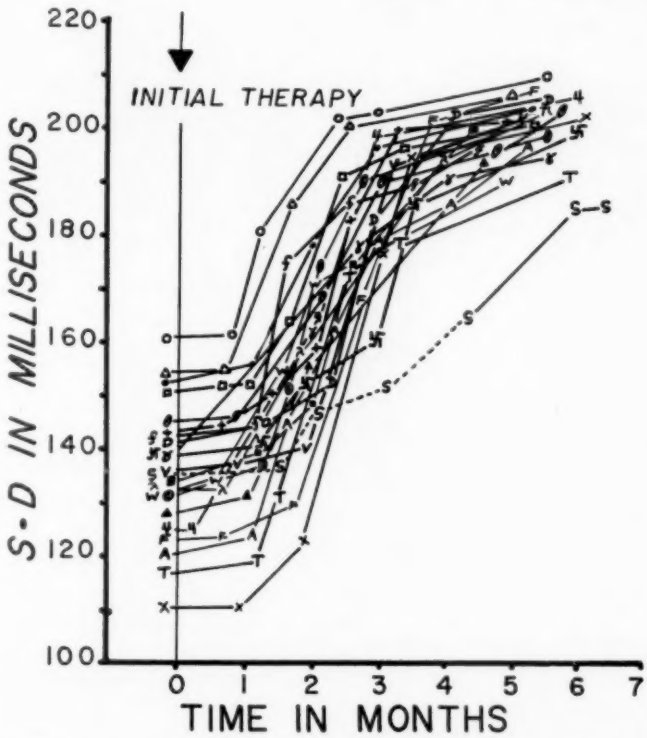

Fig. 3.—Muscle contraction time prolongation during treatment with radioactive iodine.

CLINICAL MATERIAL. The patients in this study were all clearly hyperthyroid clinically and by at least two standard tests of thyroid function which included the I_{131} uptake, I_{131} conversion ratio, serum protein bound iodine and basal metabolic rate. All patients showed a satifactory response to therapy.

In the 44 patients studied, the definitive form of therapy was surgery in 18, radioactive iodine in 22 and thiourea compounds in 4.

Results. The results of treatment with radioactive iodine, insofar as muscle contraction time is concerned, are presented in Fig. 3. The similar results of treatment with preoperative thiourea compounds and surgery are presented in Fig. 4. The 4 patients treated with propylthiouracil alone differed in no significant manner from the other cases shown graphically. Several interesting points can be noted in both graphs: (1) In every case there was a progressive prolongation of the Achilles reflex time during treatment which correlated well with the patient's clinical response. (2) Irrespective of the initial form of therapy, it is on the average 4 to 6 weeks before any appreciable change in the reflex occurs. (3) Between 6 and 10 weeks after beginning therapy, a very rapid prolongation of the reflex occurs. (4) Consistent stabil-

ization of the reflex occurs after the 12th week of therapy. (5) In general, the shorter the reflex before therapy, the shorter the reflex will be after therapy.

In order to determine whether or not there was any association between the operative stability of thyrotoxic patients during surgery and the S–D (1) those with S–D intervals between 160 and 179 millisec. and (2) those with S–D intervals between 180 and 200 millisec., a marked difference was noted. In the first group (160 to 179) all 4 of the patients had both signs of operative instability. In the remaining 14 patients (180 to 200) none of the patients showed operative instability.

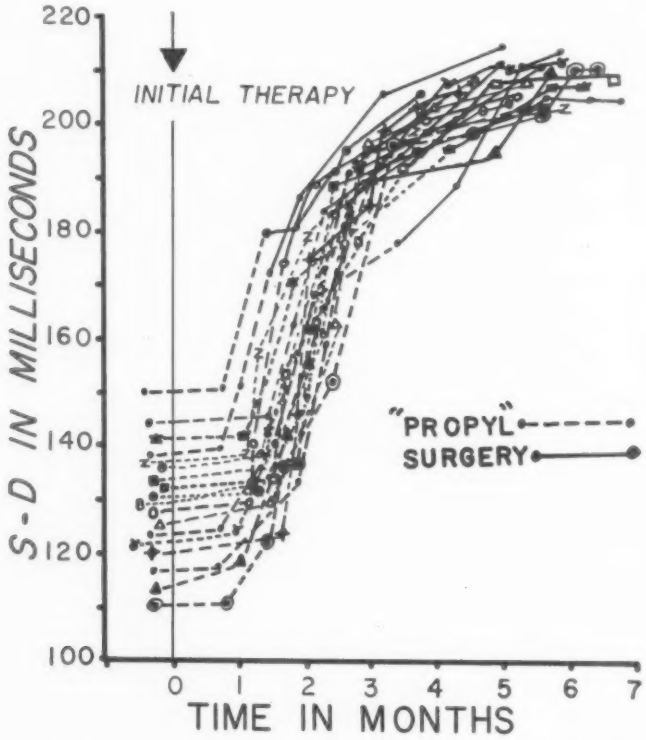

Fig. 4.—Muscle contraction time prolongation during treatment with propylthiouracil followed by surgery.

interval just prior to surgery, anesthesia records were reviewed with two measurements in mind: (1) operative tachycardia above 110 per minute, (2) a systolic blood pressure fall during manipulation of the thyroid gland of greater than 25 mm. Hg.

When the preoperative reflex measurements were divided into two groups,

Discussion. It is surprising that relatively little attention has been accorded muscle contraction in hyperthyroidism, considering that both Robert Graves and Carl von Basedow, in their original descriptions of exophthalmic goiter, noted muscle wasting and weakness as prominent findings.

At the turn of the century the creati-

nuria associated with hyperthyroidism was demonstrated by Schaffer[8], and even before that Askanazy had completed his now classic description of the histopathology of thyrotoxic myopathy[2].

While Achilles reflex slowing in the relaxation phase in myxedema has been quantitated since 1924 (Chaney[3]), we have found only one reference concerning an attempt to quantitate the rapid muscle reflexes associated with hyperthyroidism (Lambert *et al.*[4]). In that study, at the Mayo Clinic, the contraction phase was not measured, since contraction could not be precisely separated from relaxation in the monophasic curves produced by their apparatus.

In order to obviate the difficulties encountered by others, we developed the kinemometer and found that the muscle *contraction* time correlates best with the patient's clinical status. Being an endorgan response, it is particularly suited to following the patient's progress during treatment. It should not be used to the exclusion of the other better known tests of thyroid function, but does serve a useful function in the total appraisal of the patient particularly where there are conflicting data by the standard tests.

As an example, in 4 of the patients treated with radioactive iodine the uptake values remained high after treatment, although the patients were euthyroid clinically and by the Achilles reflex test. This experience is not unusual, since it has been shown repeatedly that irradiation affects the iodine organification mechanism in the thyroid gland more than the iodine trapping mechanism (Rall[7]).

Another group of patients in which the Achilles reflex test has proven of value was recently categorized by Adelman[1] using the kinemometer. He discovered a number of mildly hypothyroid patients who presented clinically as cases of hyperthyroidism.

Summary and Conclusions. By the use of a new instrument, the kinemometer, the muscle contraction time of 44 hyperthyroid patients was studied before and during treatment for their hyperthyroidism. Eighteen of the patients were treated surgically, 22 with radioactive iodine and 4 were treated with blocking agents.

In this series the surgical patients who had an Achilles reflex contraction time of less than 180 milliseconds preoperatively showed physiological instability during surgery in comparison with patients with a contraction time greater than 180 milliseconds.

In every case the Achilles reflex lengthened during treatment and there was a good correlation with the patient's clinical status. The reflex test helped to resolve several problems relative to the degree of response to therapy in some patients when there was conflict among some of the conventional tests as therapy progressed.

It is not felt that the reflex test should be used to the exclusion of other tests but that it should be used in conjunction with all available tests at all stages of diagnosis and treatment so as to get the clearest picture of the patient's overall thyroid-metabolic status.

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SUMMARIO IN INTERLINGUA

Le Libere Reflexo Achillean Durante Tractamento De Hyperthyroidismo

Per medio de un nove instrumento, le cinemometro, le tempore del contraction muscular de 44 patientes hyperthyroide esseva studiate ante e durante le tractamento de lor hyperthyroidismo. Dece-octo del patientes esseva tractate chirurgicamente, 22 esseva tractate con iodo radioactive, e 4 esseva tractate con agentes blocante.

In iste serie, le patientes chirurgic qui habeva ante le operation un tempore de contraction in le reflexo achillean de minus que 180 millisecundas manifestava instabilitate physiologic in comparation con le patientes chirurgic con un tempore de contraction de plus que 180 millisecundas.

In omne casos le reflexo achillean se prolongava durante le tractamento. Esseva notate un bon correlation con le stato clinic del patiente. Le test del reflexo esseva de adjuta in le solution de plure problemas relative al grado del responsa therapeutic in certe patientes in qui le tests conventional monstrava resultatos contradictori in le curso del therapia.

Es formulate le conclusion que le test del reflexo, que non debe esser recommendate como reimplaciamento del altere tests, pote esser usate in conjunction con omne le altere disponibile methodos de investigation a omne le stadios del diagnose e del tractamento, assecurante assi le obtention del plus precise idea possibile del stato thyroido-metabolic general que le patiente ha currentemente attingite.

LENIC FATTY ACID COMPLEX IN THE TREATMENT OF HYPERCHOLESTEROLEMIA

THE EFFECT OF A STABLE FATTY ACID MIXTURE CONTAINING THE HIGHER BONDED LONG CHAIN POLYUNSATURATED ESTERS UPON THE CHOLESTEROL BLOOD LEVELS OF PATIENTS WITH HYPERCHOLESTEROLEMIA

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While the relationship of elevated blood cholesterol levels to the occurrence of atherosclerosis and particularly coronary artery sclerosis is still a matter of controversy (Shaffer[26], Wilkinson, Blecha and Reimer[33]) so far as the individual case is concerned, there appears to be little or no question as to such relationship when applied statistically to large population groups (Ahrens *et al.*[4], Keys[16]). Even within our own population, which indulges in a relatively high fat diet, significant differences in the incidence of coronary disease have been repeatedly demonstrated in respect to individual cases and groups (Hardinge and Stare[14]) of patients with elevated versus normal blood cholesterol levels. It stands to reason, therefore, that while the maintenance of a normal cholesterol level is not *per se* complete insurance coverage for the individual against coronary disease, it at least gives a modicum of assurance as based on statistics, and may reduce to some degree the emotional stress, in itself very probably an important contributing factor in the occurrence of such episodes.

It has been suggested by several prominent nutritionists that we should, as a nation, try to reduce our dietary fat intake (Ahrens, Blankenhorn and Tsaltas[3], Beveridge *et al.*[6], Kinsell *et al.*[17]), as the relationship between a high dietary fat and hypercholesterolemia is pretty generally conceded. However, acceptance of such a possible solution to the problem is not practical. Neither this country nor any other country with a high economic standard of living is going to change its eating habits. Therefore, the problem resolves itself into finding a practical solution to the high cholesterol content of our blood in spite of our elective high fat dietary intake. It is with this objective in mind that we have approached the problem experimentally.

In a previous study (Worne and Smith[39]) from this laboratory, it was shown in a series of relatively short term human experiments with pure methyl and ethyl esters of the polyunsaturated fatty acids, that, gram for gram, a more pronounced cholesterol depressant effect was obtained with the higher 4, 5, and 6 double bonded

fatty acids than with those containing only two or three double bonds. These findings validated the concept that the degree of unsaturation was the more significant factor in the activity of the essential unsaturated fatty acids. Kinsell's recent report[18] is in accord with this hypothesis, as he demonstrated that arachidonic acid was significantly more effective than linoleic acid in reducing blood cholesterol levels in well controlled human dietary studies.

While our above cited investigations involved the use of the pure esters, it was recognized that their preparations was impractical on any large scale production, both because of cost and because of their extreme sensitivity to heat. On the other hand, there was an almost unlimited supply of the higher unsaturated fatty acids available in the form of crude glycerides and phosphatides from animal, fish and vegetable sources. These could be processed by low temperature fractionation and chromatographic separation into relatively pure fractions and stabilized so that their physical constants could be maintained within 5% of the initial established standards for an indefinite period.

Furthermore, it has been fairly well established (Reiser[24]) that a mixture of the various essential polyunsaturated fatty acids comprising the 2,3,4, 5, and 6 double bonded derivatives exhibits a biological activity ratio of 6.2:1 and is more effective in raising the total blood unsaturated fatty acid level to the so-called normal range, so that such a mixture should prove to have a maximal effect. In our experience (Worne, Scinta and Hausman[38]), it is only when these "normal" levels are reached that any significant cholesterol reducing action of the unsaturated fatty acids is noted. These factors may account in part for some of the discrepancies found in the literature as to the effectiveness of the various linoleic preparations used experimentally both in animals and man.

In the course of some of our earlier preliminary studies (Worne, Greenleaf and Pratt[37]), a case of hypercholesterolemia and peripheral vascular disease complicated with psoriasis was given the above mentioned stabilized fatty acid mixture, along with nicotinic acid as a vasodilator. The short term serial blood assays showed such startling reductions in the cholesterol levels both in respect to time and magnitude that further studies were indicated to see if this were an isolated phenomenon, or a finding which would be applicable to the average case of hypercholesterolemia. It was of course recognized that nicotinic acid alone had been reported by several investigators to be a cholesterol depressant by itself (Eilert[9]), but the possible synergistic or potentiating action of the two agents in combination appeared to require additional data. For that reason, a supplementary series of cases treated in this manner are included in this report.

Methods and Materials. Fifty patients, both male and female, all with cholesterol levels of over 275 mg. per 100 ml., with and without hyperlipemia, were chosen to evaluate the effects on pathologic blood cholesterol levels of the stabilized and highly unsaturated fatty acid glycerides prepared by low temperature fractionation and chromatographic separation techniques (Lenic Complex) alone and in combination with nicotinic acid. The formula hereinafter described as the Lenic Complex was encapsulated in 1 gm. (16 minim) capsules*. Other capsules of identical physical characteristics but containing mineral oil were prepared for use as placebos.

Lenic Complex

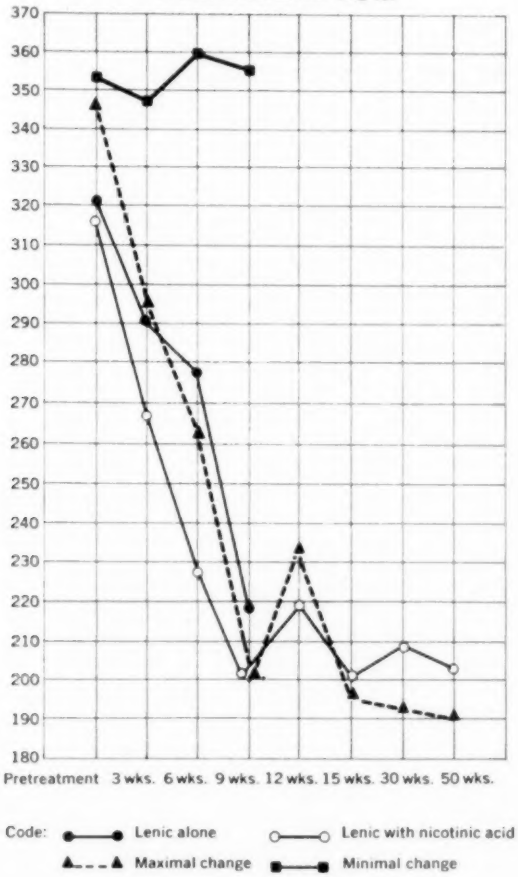
Tetraenoic, Pentaenoic and Hexaenoic acids	100 mg.
Linolenic acid	20 mg.
Linoleic acid	495 mg.
Oleic acid	175 mg.
Saturated fatty acids	100 mg.
Nonsaponifiables	10 mg.

*Lenic® Capsules, Crookes-Barnes Laboratories, Inc., Wayne, N.J.

The experimental subjects were divided into two groups composed of 25 each. In Group I, postprandial blood specimens were collected prior to therapy, at 3 weeks, at 6 weeks and at 9 weeks. Each patient was given a 1 gm. capsule of the Lenic Complex four times daily for 9 weeks.

In both groups, each of the blood specimens was assayed for cholesterol by the method of Schoenheimer and Sperry[25] and phospholipids by the method of Subbarow and Fiske[30]. In addition, each of the collected blood samples was assayed for Vitamin A, thiamine, riboflavin, ascorbic acid, tocopherols, unsaturated fatty acids, total lipids, calcium, phosphorus, sodium, potassium, manganese, zinc, iron, protein bound iodine, and total protein. The results of these assays and their correlation with the clinical observations will be published at a later date.

FIGURE 1
CHOLESTEROL LEVELS (mg.%)



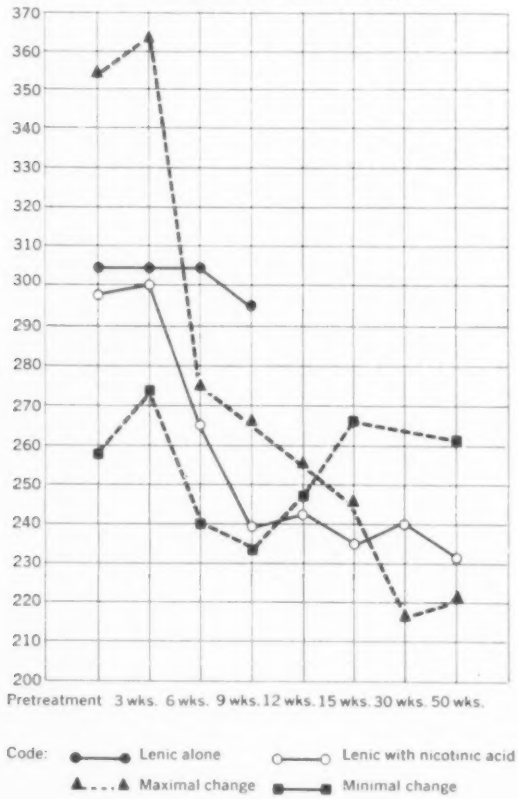
In Group II, postprandial blood specimens were collected prior to therapy, at 3 weeks, at 6 weeks, at 9 weeks, at 12 weeks, at 15 weeks, at 30 weeks and at 50 weeks. Each patient was given a 1 gm. capsule of the Lenic Complex plus 100 mg. of nicotinic acid four times a day for 50 weeks, except from the ninth to the twelfth week, when placebo therapy was introduced in place of the Lenic® Complex and nicotinic acid.

All of the patients used in this study were ambulatory and not under rigid dietary restrictions. Each patient kept a calorie counter to record the daily food intake. From this

record the fat calories in the food could be approximated. No patient with diabetes mellitus, thyroid disorders or renal disorders were accepted for inclusion in this study.

Results. The cholesterol levels of both groups are summarized in Fig. 1. More complete analysis of the cases from Group I revealed that 72% of the cholesterol:phospholipid ratio. In the remaining 20% of the cases, little or no reduction in blood cholesterol was encountered and phospholipid levels were not appreciably altered. Side effects or discomfort as a result of treatment with the polyunsaturated fatty acids (Lenic Complex) were not observed

FIGURE 2
PHOSPHOLIPID LEVELS (mg.%)



cases demonstrated an atherogenic cholesterol:phospholipid ratio prior to therapy. In 80% of the cases receiving a 1 gm. capsule of the Lenic Complex four times daily, significant reductions were observed in total cholesterol levels. There were concomitant changes in blood phospholipid concentrations which resulted in an antiatherogenic

in this study. In similar fashion, the phospholipid levels are summarized in Fig. 2.

Analysis of the findings from Group II revealed that 78% of the cases demonstrated an atherogenic ratio prior to therapy. What we believe can justifiably be considered a positive synergistic relationship was demonstrated

between the Lenic Complex and nicotinic acid during 50 weeks of therapy. All of the cases manifested significant reductions of total blood cholesterol coupled with increased phospholipid synthesis, resulting in a physiologic antiatherogenic cholesterol:phospholipid ratio. The replacement of the Lenic Complex and nicotinic acid with mineral oil placebos between the ninth and twelfth week produced a gradual increase in the blood cholesterol levels. Reinstitution of the Lenic Complex and nicotinic acid therapy at the end of the twelfth week reversed the increase observed during the placebo period and resulted in a renewed decrease of the blood cholesterol.

Side effects were limited to initial mild flushing in some of the cases, as a result of too rapid absorption of the nicotinic acid. The administration of the nicotinic acid after meals eliminated this problem. During the 50 week experimental period, it was not necessary, even once, to interrupt therapy because of the nicotinic acid dosage level.

Discussion. At the present writing, as in the case of the significance of hypercholesterolemia *per se*, there is a division of opinion relative to the physiologic importance of the cholesterol:phospholipid ratio. One group, among which we are numbered, subscribes to the hypothesis that at least 1:1 cholesterol:phospholipid ratio must exist to maintain proper colloidal solution of cholesterol in the blood plasma so as to prevent undue precipitation of the more saturated cholesterol esters in the tissues of the body, and especially in the arterial and aortic walls. Various investigators have designated this as an antiatherogenic ratio (Ladd, Kellner and Correll[19], Sinclair[27]).

Conversely, the opposing opinion denies that the ratio is of prime importance and that it has any significance. Their main argument rests on the premise that the total cholesterol figure contains both free cholesterol and ester cholesterol, substances of different solubilities (Peters and Man[22]). However, the work of Kellner, Correll and Ladd[15] has demonstrated conclusively that phospholipids play an important role in stabilizing colloidally dispersed plasma cholesterol even when the latter is present in excessive amounts.

From the clinical standpoint, establishment of the significance of the cholesterol:phospholipid ratio assumes a position of tremendous importance therapeutically. If it is not of significance, then nothing is to be gained by attempting to produce an antiatherogenic ratio by whatever dietary or chemotherapeutic means we have at our disposal. On the other hand, if it does possess merit, as we believe most of the experimental laboratory and clinical studies suggest, then every effort would be justified and every means available should be employed arbitrarily and empirically to convert an atherogenic to an antiatherogenic ratio. Figure 3 illustrates the shift of the cholesterol:phospholipid ratio in a representative case taken from each of the first and second Groups.

In this series of 50 cases there were 11 instances where a cholesterol:phospholipid ratio of better than 1:1 was present before therapy was started and this was maintained during the 9 weeks of observation.

In 4 cases in the Lenic Complex series, 4 of the 5 cases who did not show any significant reduction of their cholesterol levels, nor of their phospholipid levels during the study, showed a ratio of less than 1:1 at the beginning of the study and it remained on the negative or atherogenic pattern throughout the 9 weeks of the study. One of the 5 cases showed an insig-

nificant shift to slightly better than 1:1.

The remaining 34 cases all presented an initial atherogenic index before treatment was started with a cholesterol:phospholipid ratio of greater than 1:1. All of these ratios were converted to the anti-atherogenic pattern within a 3 to 6 weeks period with one exception, which required 9 weeks before accomplishing it.

It should be noted that in certain instances the actual cholesterol levels may persist above the accepted 220 to 250 mg. upper level, but where this occurs, the actual cholesterol:phospholipid ratio is adequately maintained on the antiatherogenic pattern, which we believe is much more important than the actual cholesterol levels.

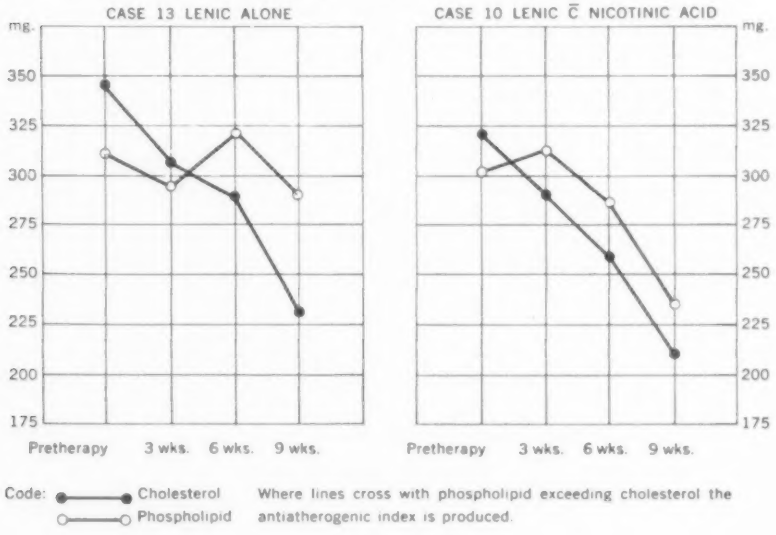
Another point which should be noted is that frequently the phospholipid level may rise initially under fatty acid therapy, and only after a favorable cholesterol:phospholipid ratio is attained does it tend to fall in parallel fashion with the cholesterol.

Unfortunately, the biochemical mechanisms involved in the interrelationship of the fatty acids, phospholipids and cholesterol are extremely complex. As was true of Einstein's theory of relativity, which was understood by a very limited number of mathematicians, so, in this case, the unraveling of the problem can only be carried out by a rather small group of investigators, especially interested and trained in the biophysical and biochemical sciences. However, during this period in which the complete answer is slowly evolving, we, as physicians, can and should take advantage of any information which becomes available.

Already there have accumulated considerable data regarding the normal biosynthesis of the several types of phospholipids found in the body, as well as their relationship to the polyunsaturated fatty acids. At the risk of oversimplification, let us review a few of the highlights of these data. The phos-

FIGURE 3

CHOLESTEROL—PHOSPHOLIPID RATIOS IN TYPICAL UNSELECTED CASES



pholipids (consisting of the lecithins, sphingomyelins and cephalins), are synthesized chiefly in the liver, with some minor contributions from the kidneys and intestinal tract (Bollman, Flock, Cain and Grindley[7]). About 95% of the phospholipids are formed as lecithin and sphingomyelin. Only approximately 5% of them are cephalins (Worne[36]). They require the mediation of several important enzymes for their production, especially choline oxidase (Handler and Bernheim[13]), Co-enzyme A and ATP. This becomes of importance clinically in the case of liver damage where their rate of formation is retarded or inhibited (Gertler, Garn and Lerman[12]). Other causes of diminished formation are the result of excessive cholesterol ingestion (Patterson, Keevil and McHenry[20]) and deficiencies of choline, thyroxin (Flock, Bollman and Berkson[11]) and the polyunsaturated fatty acids, while their production may be stimulated by the administration of the latter substances (Diluzio and Zilversmit[8], Pearlman, Stillman and Chaikoff[21], Platt and Porter[23]).

The lipid portion of the phospholipids is made up primarily of a mixture of saturated and unsaturated fatty acids in a fairly constant ratio (Sinclair[28], Ada[1]). Any variation in the iodine number of these phospholipids is dependent entirely upon the degree of unsaturation and not from a variation in the percentage of the unsaturated acids in the molecule (Sinclair[29]).

Radioactive phosphorus (Fishler, Entenman, Montgomery and Chaikoff[10]) and tagged fatty acids (Weinman, Chaikoff, Entenman and Dauben[32]) confirm the hepatic source of the phospholipids, chiefly from the large cytoplasmic granules of the liver cells, and show a very rapid turnover at a rate of about 5% an hour (Balfour[5]). Adrenal steroids or corticotropic hormone (ACTH) will increase the formation of the phospholipids (Adlersberg, Schaefer and Dritch[2]), while induced adrenal insufficiency will cause their diminution or repression (Zilversmit, Stern and Overman[40]).

More important than these broad generic observations is the specific role which the essential polyunsaturated fatty acids play in phospholipid formation. Deficiency of these fatty acids results in an inhibition of the synthesis of the intermediate phosphorus bearing lipids to phospholipids. Pyridoxine or liver damage likewise may prevent the conversion of the double bonded linoleic acid or the triple bonded linolenic acid to the physiologically active tetra, penta and hexaenoic derivatives which are necessary for the final formation of certain physiologically active forms of the phospholipids. On the basis of serial blood assays in patients reflecting lipid blood dyscrasias as exemplified by the accompanying cases, we believe that polyunsaturated fatty acid deficiency may be the main factor behind the atherogenic lipid levels and ratios observed in hypercholesterolemia and we believe the administration of the higher bonded acid mixtures is the most practical approach to the problem on the basis of our present knowledge.

In the preceding paragraphs we have discussed some of the theoretical aspects relating to the formation of the phospholipids and the significance of maintaining a normal antiatherogenic cholesterol:phospholipid ratio. At this point we would like to make certain empiric clinical observations based on our personal experiences.

In the course of one of our investigational programs, a group of rheumatoid arthritics, with previously normal cholesterol:phospholipid ratios, evidenced a metabolic deterioration, all within a short period of time. Investi-

gation of the phenomenon revealed that each of the patients demonstrated a toxicosis resulting from the intake of DDT, Lindane and Chlordane in a particular seasonal foodstuff. These enzyme inhibitors, by either reducing the synthesis of the essential phospholipids or increasing their rate of metabolic destruction, permitted a lipid imbalance to occur, which eventuated in an atherogenic cholesterol:phospholipid ratio.

It has been observed that in cases of healed myocardial infarction, if the levels of the phospholipids could not be raised to establish a proper antiatherogenic ratio with cholesterol, additional infarctions occurred in a number of these cases. Conversely, if the cholesterol:phospholipid ratio could be corrected to give an antiatherogenic ratio, succeeding infarctions were not observed as long as this ratio was maintained.

Further studies on the 20% of the patients who did not respond to the daily intake of 4 gm. of the Lenic Complex revealed factors which may have contributed to the lack of therapeutic response. In 2 of the cases it was determined through additional studies that biliary dyskinesia, coupled with reduced bile secretion, was the responsible factor. In the remainder of the cases, it was determined that avitaminosis C was the inhibiting factor. It has been demonstrated that subnormal levels of Vitamin C results in deposition of lipid in the intima and that a localized depletion often exists in segments of arteries susceptible to atherosclerosis for reasons of mechanical stress. Adjacent segments, where mechanical stress is less, tend to have a higher ascorbic acid content and atherosclerosis is rare (Willis and Fishman[34]). Ascorbic acid deficiency in arteries with resulting ground substance depolymerization may account for the release of glucoprotein noted in the blood of subjects with severe atherosclerosis (Willis, Light and Gow[35]). An interesting observation during the course of therapy with the Lenic Complex was the frequency with which patients reported an improvement in muscle tone. This improvement is readily understandable when it is realized that the muscle phospholipids are rich in the highly unsaturated fatty acids and that in the presence of tissue glutathione, they increase the rate of O_2 consumption by the muscle tissue (Tait and King[31]).

Summary and Conclusions. The cholesterol-lowering effects of a preparation (Lenic Complex) containing the higher unsaturated fatty acid glycerides, with 4, 5, and 6 double bonds, in addition to the two double bonded linoleic acid, were observed in 50 individuals.

Dosage of 4 one-gram capsules daily, on a moderate fat diet, for 9 weeks, gave a satisfactory drop from the previously high blood cholesterol levels in 80% of the patients. A number of these patients reported subjective improvement, in intermittent claudication and vascular stasis in those with peripheral vascular disease, and in anginal spasms in coronary insufficiency.

The administration of 100 mg. of nicotinic acid, four times daily, with the unsaturated fatty acid complex, produced a greater fall in blood cholesterol than either, given singly. Administration of the combination lowered blood cholesterol in all 25 patients and the medication was well tolerated during the period of 50 weeks, with side effects limited to mild flushing from the nicotinic acid. This was controlled by giving the capsules after meals.

A preparation containing the lower

polyunsaturated fatty acids, along with those of 4, 5, and 6 double bonds, in capsule form (Lenic Complex) gives satisfactory reduction in blood cholesterol. Better patient cooperation is obtained by the use of capsules instead of large volumes of oil. The undesirable weight gain frequently associated with the ingestion of large amounts of oils, with their high caloric content, is avoided with the concentrated preparation.

Maintenance of a proper ratio of blood cholesterol to phospholipids may be of greater significance than the absolute level of cholesterol alone, in preventing cholesterol deposition in arteries. The unsaturated fatty acids are essential for optimum phospholipid synthesis.

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SUMMARIO IN INTERLINGUA

Complexo Lenic de Acido Grasse in le Tractamento de Hypercholesterolemia Le Effecto Exercite per un Stabile Mixtura de Acidos Grasse, Continente le Polynonsaturate Esteres a Catenas Longe Tetra-, Penta-, e Hexaenoic, Super le Nivello Sanguinee de Cholesterol in Patientes con Hypercholesterolemia

Le effectos cholesterolo-reductori de un preparato (Complexo Lenic) continente le glyceridos de nonsaturate acidos grasse a 4, 5, e 6 ligationes duple si ben como etiam acido linoleic con su duo ligationes duple esseva observate in 50 subjectos.

Un dosage de 4 capsulas de un gramma cata un per die durante un periodo de 9 septimanas, combinate con un dieta a contento moderate de grassia, resultava in un reduction satisfactori del previemente alte nivellos sanguinee de cholesterol in 80% del patientes. Un numero del patientes reportava melioration subjective, tanto in claudication intermittente e stase vascular in casos de morbo periphero-vascular como etiam in spasmos anginal in casos de insufficientia coronari.

Le administration de 100 mg de acido nicotinic, quatro vices per die, insimul con le complexo de nonsaturate acidos grasse produceva un plus marcate reduction del nivellos sanguinee de cholesterol que le administration del complexo sol e etiam que le administration del acido nicotinic sol. Le administration del combination de Complexo Lenic e acido nicotinic reduceva le contento de cholesterol in le sanguine in omne le 25 patientes assi tractate. Iste regime esseva ben tolerate durante le periodo de 50 septimanas de su application, e le adverse effectos lateral esseva limitate a leve grados de fluxion como effecto del acido nicotinic. Isto esseva eliminate per le administration postprandial del capsulas.

Un preparato continente le basse polynonsaturate acidos grasse insimul con illos a 4, 5, e 6 ligationes duple, administrate in le forma de capsulas (Complexo Lenic), resulta in un satisfacente reduction del contento sanguinee de cholesterol. Le cooperation del patientes es assecurate plus facilemente in le uso de capsulas in loco de grande volumines de oleo. Le non-desirabile augmento del peso que es frequentemente associate con le ingestion de grande quantitates de oleo a alte contento caloric pote esser evitate per le uso de un preparato concentrate.

Le mantenentia del correcte proportion inter le cholesterol e le phospholipidos del sanguine es possibilemente plus significative que le nivello de cholesterol per se in prevenir le deposition de cholesterol in le arterias. Le nonsaturate acidos grasse es essential in le synthese optimal de phospholipidos.

A NEW NONAMPHETAMINE ANORECTIC AGENT

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In recent years there has been a marked shift in emphasis away from the role of endocrines in obesity toward an awareness of other pertinent causative factors commonly observed in obese patients. Medical attention is now being focused more sharply on emotional, environmental and sociological factors as potent motivating forces in excessive eating (Freed[3]). Some consideration should also be given, however, to individual constitutional and metabolic abnormalities that may predispose to overweight despite relatively normal food intake (Freed[4]). Perhaps one of the best definitions of the term "obesity" is that offered by Bauer[1] who stated that obese individuals are those persons who, when left to their own automatic regulation of diet and activity, exhibit a compulsory tendency toward a pronounced and abnormal accumulation of fat. The general acceptance of this latter concept by physicians has resulted in an unprecedented attack on the obesity front. Physicians are no longer hesitant to prescribe medications that effectively aid the patient in diet restriction. Effective medication combined with intelligent medical supervision has produced far more successful results than the old admonitions and cliches such as "push yourself away from the table," and the like. For it is recognized that appetite is a strong primitive emotion and, as such, cannot be easily subdued with well-intentioned advice.

The amphetamine compounds are being used with considerable success in obesity control, especially when combined with medical and psychiatric management designed to eliminate various tensions and other disturbances (Kroger and Freed[6]). Nevertheless, pharmacologic research has continued in a search for drugs which are equal to or superior to the amphetamines in appetite suppression, and yet minimize the unpleasant side reactions associated with central nervous overstimulation. A new drug, 2-phenyl-*tert.*-butylamine resinate‡, which is chemically and pharmacologically different from amphetamine has recently been developed and has been supplied for clinical evaluation of its appetite suppression activity and its side effect. The formula of the drug is schematically represented below.

The drug is a structurally symmetrical amine exhibiting pharmacologic properties of the sympathomimetic drugs yet differing from those commonly used in appetite suppression today. As a result of considerable pharmacologic experience, certain generalizations can be made relating structure of the drug to its potential

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‡This drug (Ionamin) was supplied by the R. J. Strasenburgh Company.

pharmacologic activity. The following are among the more pertinent observations: 1) An increase in the number of carbon atoms in the side chain decreases the pressor potency. 2) An increase in the number of carbon atoms in the side chain increases the oral effectiveness. 3) When more than three carbon atoms separate the amine nitrogen from the ring, toxicity is increased. 4) The presence of a hydroxyl group, either on the side chain or the ring, increases the pressor potency. 5) End methylation increases both the pressor effect and bronchial dilatation.

Application of the above generalities to 2-phenyl-*tert.*-butylamine (Ionamin) leads one to expect that this drug will exhibit minimum pressor activity, increased oral potency, minimum toxicity and essentially no bronchial dilatation.

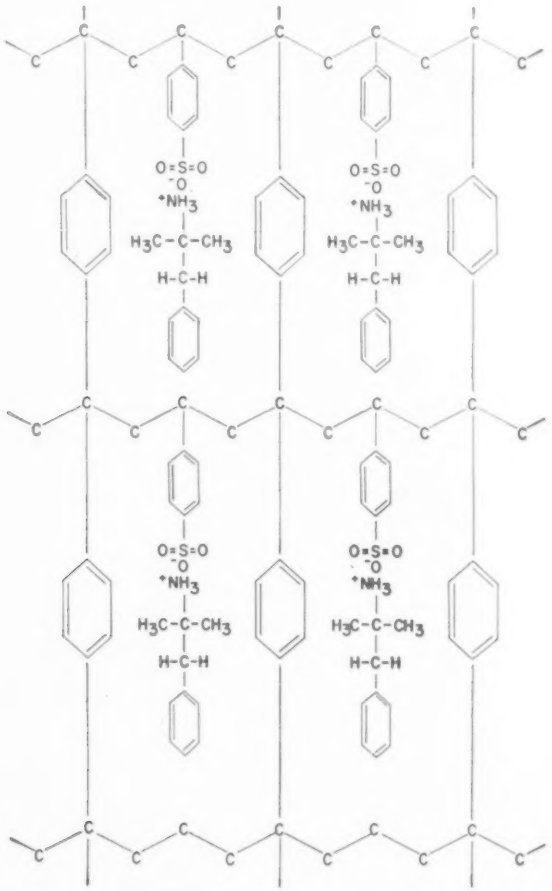

Fig. 1.—Schematic representation of 2-phenyl-tert.-butylamine (Ionamin).

Laboratory data further demonstrate that the active drug is released from the resin complex at a predictable and therapeutically satisfactory rate. These data were obtained by means of the

in-vitro percolation technique previously developed for the purpose of studying drug release from resin complexes (Becker and Swift[2]) and are shown in Table 1. The *in-vitro* experimental data indicate an initial high level release of the drug in gastric juice followed by a reduced but prolonged rate of release in gastrointestinal fluids. Clinically, therefore, Ionamin will provide an effective pharmacologic concentration within an hour following medication which should be maintained for an 8- to 9-hour period by the additional amounts of drug released in the gastrointestinal tract.

TABLE 1.—PERCENT OF TOTAL DRUG RELEASED AT THE FOLLOWING HOURLY INTERVALS

Release Fluids	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Simulated gastric juice	20	4	12	8	9	8			
Simulated intestinal juice				9	0	5	7	4	1	2	9	2	2	1	5

Methods. In the clinical evaluation of appetite suppression, the multiple dosage level method of Freed, Keating and Hays[5] has been utilized. This procedure avoids, to a considerable extent, the need for placebo controls or double blind procedures normally considered necessary to overcome the factor of suggestion inherent in the doctor-patient relationship. This latter factor has, in various studies, based upon subjective response, accounted for about 35% of the patients reporting positive results. A reliable therapeutic result is claimed only when 70% or more patients respond favorably in the type of study reported here.

A single change has been made in the previously used multiple dosage level technique. Ordinarily a large group of patients chosen at random are administered drugs at various dosage levels, and the therapeutic results and incidence of side reactions are analyzed. However, it is common experience, when prescribing appetite suppressants and other drugs, to find that there are some patients who are relatively resistant, others who are highly sensitive, and still others who have an average response to the drug. For this reason, an attempt was made to determine beforehand into which category the patient would fall. The sensitive patients were placed on either the 15 mg. of 22 mg. capsules once daily in the morning. Patients in the average category were administered a 30 mg. capsule once a day. The suspected resistant patients were placed on 44 mg. and 60 mg. doses once a day. While it is acknowledged that a clinical estimate of a patient's responsiveness was sometimes inaccurate, such a technique is constantly utilized by clinicians in office practice to avoid unnecessary delay in instituting treatment.

Results. An evaluation of the patients' appetite suppression at the different dosage levels is presented in Table 2. The clinical response was graded as being excellent, satisfactory or poor. It can be noted that significant therapeutic response was obtained at all dosage levels ranging from about 70% at the 15 mg. dose to about 80% at the 60 mg. dose level. These estimations are conservative since they do not include those patients who reported a fair degree of appetite suppression.

The data relative to weight loss in a group of patients receiving the 30 mg. and 60 mg. daily doses of Ionamin were collected and calculated from the patients' weight charts. The data are presented in Table 3. These data indicate a significant weight loss amounting to approximately 0.25 lb. per patient per day.

Data relative to incidence and severity of side reactions during Ionamin medication were collected and evaluated on the basis of the patients'

reports. While these observations are obviously subjective, it was felt by the observer that they were essentially reliable. The incidence and severity of side reactions encountered are summarized in Table 4.

Discussion. The effect of appetite suppression in some of these individuals was compared with the effect of absence of the stimulating effect with Ionamin which they had previously experienced with amphetamine. There was freedom from muscle tension and from the nervousness which they had encountered with the latter drug. Many patients have reported that they were unaware of any subjective response following the administration of the

TABLE 2.—EVALUATION OF APPETITE SUPPRESSION WITH IONAMIN

Ionamin Dosage (mg.)	*No. of Patients*	*Number of Patients with the Following Appetite Suppression Response*			
		Excellent	*Satisfactory*	*Fair*	*Poor*
15	17	5	7	3	3
22	44	9	24	5	6
30	60	19	28	9	4
44	22	13	4	3	2
60	35	18	11	4	2

TABLE 3.—SUMMARY OF WEIGHT LOSS DATA

Ionamin Dosage (mg.)	*No. of Patients*	*Average Initial Weight*	*Total Patient Days*	*Total Pounds Lost*	*Average Weight Lost (lbs./pt./day)*
30	60	171 4	1674	410 5	0 25
60	26	192 5	913	239 0	0 25

TABLE 4.—OCCURRENCE OF SIDE REACTIONS TO IONAMIN

Ionamin Dosage (mg.)	*No. of Patients*	*Number of Patients Having the Following Level of Side-reaction*		
		Severe	*Moderate*	*Mild*
15	17	0	0	0
22	44	1	1	0
30	60	3	3	3
44	22	0	3	1
60	35	2	2	3

prior medication with amphetamines. It appears that the clinical response to a 30 mg. dose of Ionamin is somewhat superior to a 15 mg. daily dose of dextro-amphetamine in a sustained release form. There also seems to be a definite qualitative difference in response between Ionamin and amphetamine. Many patients reported an Ionamin capsule, and they were pleasantly surprised by their loss of appetite at mealtime. This lack of overstimulation following Ionamin medication was most appreciated by those patients who were anxious, nervous and tense. Amphetamine administered to these patients was disturbing but had been accepted because of the im-

portance of its appetite-curbing properties. Some of the patients included in this study were refractive to further weight loss with amphetamines but were able to continue their weight loss when placed on high doses of Ionamin.

The chief side reaction was insomnia. This insomnia was somewhat different from that which had been encountered with amphetamine therapy. The patients reported a wakefulness which was not unpleasant, compared to the nervous over-exhilaration which had prevented sleep following amphetamine treatment. In addition to the insomnia, there was an occasional report of nausea which was interpreted as an over-extension of the therapeutic effect and an occasional complaint of dryness of the mouth on the higher dosages. Constipation was reported in about 10% of patients, which approximates the findings on amphetamine therapy. Only 6 patients in the entire study reported nervousness and agitation to the point of intolerance. An interesting observation can be made from the table on side reactions in that there were more serious side reactions at the 30 mg. level than at either the 44 mg. or even 60 mg. levels. This probably is due to the fact that the resistant patients were accurately chosen for the higher dosages, while at the 30 mg. level some sensitive patients were inadvertently selected. On the other hand, it can be reported that 9 of the 60 patients taking 30 mg. daily reported considerably less nervous tension than after taking a comparable therapeutic dose of dextroamphetamine (15 mg.). Six of the 35 patients at the 60 mg. level reported a similar gratifying absence of tension with Ionamin. At the 22 mg. and 15 mg. levels, the patients reported little or no tension, palpitation, exhilaration or other symptoms which they had previously experienced when taking relatively moderate amounts of amphetamine.

Summary. A series of 178 patients were administered a new nonamphetamine long acting anorectic drug, 2-phenyl-*tert.*-butylamine resin (Ionamin) for purpose of weight reduction. A total of 2587 patient days experience with Ionamin was clinically evaluated. A weight loss of approximately 0.25 lb. per patient per day was obtained. This new drug effectively suppresses appetite and does so with a significantly lesser incidence of side effects than is experienced with equivalent therapeutic doses of amphetamine. Individuals whose weight had plateaued with the use of other anorexigenic agents have responded satisfactorily to this agent.

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EFFECT OF COMBINED ADMINISTRATION OF AMINO-BINDING SUBSTANCES IN HEPATIC ENCEPHALOPATHY*

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Considerable attention has been redirected to the metabolic disturbances responsible for central nervous system dysfunction in advanced hepatic disease. The most popular current belief incriminates the elevated blood ammonium level frequently observed in this condition although the precise relationship is not clear, if indeed its etiologic significance is accepted. Certainly it has been repeatedly demonstrated that there is no quantitative relationship between the degree of blood ammonium elevation and the severity of any attending neurological disturbances (Fazekas *et al.*[3], Summerskill, Wolfe and Davidson[13]). This has been particularly evident when the blood ammonium level is manipulated through reduction by administration of certain ammonia-binding amino acids (Fazekas, Ticktin and Shea[4,5], Sherlock, Summerskill and Dawson[12]).

In previous studies the administration of monosodium l-glutamate and l-arginine individually (Fazekas, Ticktin and Shea[4,5]) failed to produce clinical remission in an appreciable number of subjects nor was there any demonstrable improvement in the impaired cerebral oxygen consumption characteristic of hepatic encephalopathy (Fazekas *et al.*[3]). It has been reported that a combination of l-arginine and monosodium l-glutamate will in animals confer protection against induced ammonium toxicity (Winitz *et al.*[14]); and it was, therefore, decided to extend this experimental observation to patients with hepatic encephalopathy and an elevated blood ammonium level.

Method. The studies herein described were performed on 11 patients with Laennec's cirrhosis presenting clinical signs and symptoms of hepatic encephalopathy. The state of consciousness ranged from lethargy to deep coma; the conscious patients in addition to their lethargy were confused and incoherent.

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The mixture of l-arginine and monosodium l-glutamate consisted of 25 gm. of l-arginine and 22.5 gm. of monosodium l-glutamate per liter of 5% glucose and water and was infused over periods ranging from 5 to 11 hours in all but one instance in which the infusion was continued for 24 hours.

In 8 of the patients, cerebral hemodynamics and total cerebral oxygen consumption ($CMRO_2$) as well as arterial and cerebral venous ammonium concentrations were performed before and repeated within 2 to 3 hours after the infusion was started. The cerebral ammonium utilization was also calculated in most instances.

In all the above patients, and in 3 additional subjects with hepatic encephalopathy, arterial blood ammonium levels were determined at ½, 1, 2, 3, and 5-hour intervals during infusion of the amino acid mixture, and in a number of instances values at 24 and 48 hours were also obtained.

Scheinberg and Stead's modification[10] of Kety and Schmidt's procedure[6] for the determination of cerebral blood flow (CBF) was applied in this study. The oxygen content of the blood was determined by the manometric technique of Van Slyke and Neill[8]. Mean arterial pressure (MAP) was obtained directly from the femoral artery by means of a damped aneroid manometer (Alman and Fazekas[1]). Blood ammonium levels were determined by a microdiffusion nesslerization method modified from Seligson[11] on freshly drawn blood from the femoral artery and the jugular bulb. Blood was drawn without stasis into a previously calibrated 2 ml. syringe, and 1 ml. specimens were injected into each of two Seligson microdiffusion vessels within 15 to 45 seconds after withdrawal. In all cases a water blank was run with each pair of arterial and venous samples. The cerebral ammonium utilization was calculated using the formula:

$$\frac{\text{CBF} \times \text{Arterial-cerebral venous ammonium difference}}{100}$$

Results. Table 1 presents the results of the cerebral hemodynamic and metabolic studies as well as the arterial and cerebral venous blood ammonium concentrations and cerebral ammonium utilization before and during the infusion of the amino acid mixture.

The results demonstrate a slight but significant increase of both the rate of cerebral blood flow and total cerebral oxygen consumption associated with the administration of the arginine-glutamate mixture. The latter values, nevertheless, were still considerably reduced from values obtained in normal alert subjects. There was no change in cerebral vascular resistance or mean arterial pressure. A significant decrease in both arterial and cerebral venous ammonium concentration was noted as has also been found to accompany the individual administration of l-argmine and monosodium glutamate. In no case was there evidence of excessive cerebral ammonium production, and the changes in ammonium utilization were neither predictable nor constant. It should be noted that the pH varied between 7.37 and 7.44 before the administration of the combination of ammonia-binding compounds, and that there was no significant change following administration.

Table 2 presents the findings of a more detailed following of the arterial ammonium level in all of the patients in the present study. In all instances, a significant reduction ($p<.05$) was noted within one-half hour after the beginning and maintained for 5 hours during the infusion. In the 5 patients in whom the ammonium levels were determined 39, 40, 41, and 43 hours after termination of the infusion, the level was still somewhat depressed below pre-treatment values. Three of the patients exhibited definite clinical improvement in cerebral functions during the infusion of the amino acid mixture. Of the 11 patients treated, 9 expired, and 2 improved sufficiently to permit discharge from the hospital.

Discussion. As has been noted in previous studies using monosodium l-

glutamate and l-arginine individually, the reduction in blood ammonium concentration attendant upon their administration is not usually accompanied by significant clinical improvement. The present findings again emphasize the apparent lack of correlation between arterial blood ammonium values and clinical state and suggest the possibility of other as yet unknown etiologic factors operating in this condition.

could not be related to the clinical condition of the patients, either before or after administration of the arginine-glutamate mixture.

It has been postulated that the failure of the individual amino acids to maintain a lowered blood ammonium level despite their continued administration in the hyperammonemic patient is the possible exhaustion of the availability of high energy phosphate compounds in the case of monosodium l-

TABLE 1.—EFFECT OF THE COMBINATION OF L-ARGININE AND L-GLUTAMATE ON CEREBRAL HEMODYNAMICS AND METABOLISM

	CBF		*$CMRO_2$*		*CVR*		*MAP*		*Arterial NH_3*		*Venous NH_3*		*NH_3 Utilization*		*Arterial pH*	
Age	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E
46	27.8	35.5	1.4	1.9	2.8	2.0	79	70	2.1	1.5	1.9	1.4	0.06	0.04	7.41	7.42
40	39.3	57.0	1.3	2.0	1.5	1.2	59	70	2.7	1.0	2.6	0.6	0.04	0.23	7.37	7.36
47	36.1	42.8	1.0	1.2	2.5	2.2	90	95	7.7	4.9	6.8	4.5	0.33	0.17	7.43	7.41
25	63.0	78.3	1.9	2.1	1.1	0.9	67	73	1.8	0.5	1.6	0.4	0.13	0.08	7.39	7.42
65	30.7	41.6	1.6	2.1	3.2	2.0	98	84	1.8	1.0	1.6	0.9	0.06	0.04		
65	34.6	29.0	1.4	1.2	1.9	2.0	64	59	1.8	1.5	1.6	1.2	0.07	0.09	7.40	7.40
34	46.5	65.1	2.1	2.3	1.7	1.2	80	75	3.7	1.7	3.5		0.09			
65	21.2	21.7	1.5	1.5	3.3	3.7	69	80	2.7	0.9	2.6	1.1	0.03	0.04	7.40	7.40
60	32.3	40.5	1.1	1.4	1.8	1.9	58	78	3.5	1.3	3.2	1.3	0.10	0	7.44	7.49
									Mean Values							
	36.8	45.7*	1.5	1.7*	2.2	1.9	74	76	3.1	1.6*	2.8	1.4*	0.10	0.08	7.41	7.41

CBF signifies cerebral blood flow in ml. per 100 gm. of brain per min.; $CMRO_2$, cerebral oxygen consumption in ml. per 100 gm. of brain per min.; CVR, cerebral vascular resistance in mm. of Hg per ml. blood per 100 gm. of brain per min.; MAP, mean arterial blood pressure in mm. of Hg; C, values before administration of combination and E, values after administration of combination.

*Significant difference, $p < .05$

It has been claimed that a superior correlation exists in such instances of blood ammonium elevation between the cerebral arterial venous ammonium difference and the degree of encephalopathy (Bessman and Bessman[2]). However, as we have pointed out, this difference is governed to a very large extent by the rate of cerebral blood flow, and if any correlation is to be found, it will necessarily be the cerebral ammonium utilization which would be the significant index of its toxicity. In the present study, even this value was highly variable and

glutamate (Fazekas, Ticktin and Shea[4], Pelner[7]), and depletion of ornithine or citruline, or both, in the case of arginine (Reynolds, Redeker and Davis[9]). The simultaneous utilization of amino acids having different pathways for incorporation of ammonium has, at least in the present studies, been more effective in maintaining reduced ammonium levels, than with either arginine or glutamate alone.

The fact that 3 of the subjects of the present study demonstrated improvement in their clinical state while the mixture was being infused sug-

TABLE 2.—EFFECT OF COMBINATION OF L-ARGININE AND L-GLUTAMATE ON ARTERIAL AMMONIUM LEVELS

	Arterial Ammonia (μg./ml.)												
	Hours								*Clinical change at time of administration*	*Subsequent clinical change*	*Final status*	*Total dosage*	
Age	*C*	½	*1*	*2*	*3*	*5*	*24*	*48+*				*Arg. (gm.)*	*Glut. (gm.)*	*Total time (hrs.)*
46	2.1	1.7	1.5	1.5	0.6	0.6	1.2	2.6	Became responsive	24 hrs. alert & oriented	Expired in 5 days	37.5	33.75	10
40	2.7	2.1	1.4	1.2	1.0	0.9	1.2	1.4	No change	48 hrs. alert & oriented	Discharged	37.5	33.75	8
47	7.7	6.4	6.8	4.9	4.8	6.7			No change	No change	Expired same day	37.5	33.75	5
25	1.8	1.1	0.6	0.5	1.5	1.7	2.6		No change	Worse	Expired in 2 days	37.5	33.75	5
65	1.8	1.6	1.4	1.0		1.2	1.8		No change			37.5	33.75	10
	1.8	1.8	1.7	1.5	1.6	1.5	2.1		No change	No change	Expired in 1 day	100.0	90.00	24
34	1.8		1.7	1.6	1.4	1.4		1.3	Responsive	Alert and oriented until given high protein		25.0	22.50	7
	3.7		2.8	1.8	1.7		2.1		Responsive & coherent	Remained alert & oriented	Discharged	45.0	47.50	8
65	2.7	2.3	1.2	0.9	1.2		2.5	1.8	No change	24 & 72 hrs., awake & alert	Expired in 2 months	25.0	22.50	5
47	1.4	1.1	1.1	1.2	0.9	0.9			No change	Bleeding	Expired in 4 days	37.5	33.75	10
54	3.7	3.3	2.6	2.1	1.8	1.4			No change	No change	Expired same day	25.0	22.50	11
29	2.2		1.9		1.0	1.3	1.3	1.7	Coherent for 3 hrs.	Coma hepatitis	Expired in 2 days	25.0	50.00	9
60	3.5	3.3	2.0	1.6	1.3	1.2	2.7		No change	No change	Expired in 1 day	37.5	33.75	11
									Mean Values					
	2.8	2.5*	2.0*	1.6*	1.6*	1.7*	1.9	1.8						

*Significant difference from control values, $p < .05$. The control means are as follows: ½-hour, 2.9; 1-hour, 2.8; 2-hour, 2.9; 3-hour, 2.9; 5-hour, 2.8; 24-hour 2.4; and 48+ hour, 2.3.

gests that a reduction of blood ammonium may have specific therapeutic value. It should be pointed out, however, that there is a fairly high incidence of spontaneous recovery in patients receiving only symptomatic care, that is, blood transfusions, a low or protein-free high carbohydrate and high vitamin diet.

We have previously expressed the opinion that in some cases of hepatic encephalopathy, ammonia may not be the only neurotoxic substance (Fazekas, Ticktin and Shea[4]). One of the 2 patients noted above who improved sufficiently to be subsequently discharged was given sufficient glycine to raise arterial blood ammonium levels to values higher than those observed when in coma without producing evidence of cerebral dysfunction. The same patient was deliberately placed on a high protein diet, and a flapping tremor and lethargy were induced with an arterial blood ammonium concentration of 3.8. The patient again rapidly improved during the administration of a mixture of arginine and glutamate. It is, of course, generally recognized that the concentration in the blood of a particular substance may not necessarily reflect the actual tissue concentration and that there usually is no fixed blood level at which central nervous system symptoms are induced. Certainly factors such as blood volume, arterial oxygen saturation, pH, carbon dioxide tension, as well as concentrations of electrolytes may influence the passage in and out of the cell of ammonia and may determine to some extent its neurotoxicity. Although substances other than ammonia may well play a role in the etiology of hepatic coma, the occasional favorable response to the administration of the amino acid mixture suggests that in certain patients the elevated blood ammonium may be the major precipitating cause. The fact that in the majority of our patients the combined administration of l-arginine and l-glutamate failed to produce significant clinical improvement seems to indicate that this condition may not be the same as induced ammonium toxicity in animals. Our findings, however, do not preclude the use of ammonia-binding amino acids as an adjunct to the treatment of hepatic encephalopathy.

The slight increase in total cerebral blood flow and oxygen utilization noted during the infusion of the combined mixture of amino acids is of questionable significance since there is no apparent correlation between the arterial blood ammonium level, cerebral oxygen consumption, or the state of consciousness in these studies. As has been previously mentioned, there may well be significant changes in the oxygen consumption of the alerting centers in the reticular formation without a detectable difference in overall cerebral oxygen utilization. Furthermore, an increase in total cerebral oxygen utilization need not be necessarily associated with a return of consciousness, as evident from the present study.

Summary and Conclusions. A mixture of 2 ammonia-binding substances, l-arginine and monosodium l-glutamate were administered to 11 patients with hepatic encephalopathy associated with Laennec's cirrhosis. Although arterial ammonium levels were found to be reduced significantly in all cases, only 2 of the patients improved sufficiently to permit discharge from the hospital. In spite of a slight increase in total cerebral oxygen consumption and cerebral blood flow, there was no correlation between these values, arterial ammonium levels, or the clinical status of the patients. It is reiterated that endogenous ammonia alone is probably not the sole neurotoxic factor in the

spontaneous encephalopathy in patients with severe liver disease. Therefore, it should not be surprising that ammonia-binding amino acids alone or in combination do not induce appreciable clinical improvement in all cases of hepatic encephalopathy. These findings, however, do not preclude their use as an adjunct in the treatment of hepatic encephalopathy.

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SUMMARIO IN INTERLINGUA

Le Effecto Del Administration Combinate De Substantias Amino-Ligante In Encephalopathia Hepatic

Un mixtura de duo substantias ammonio-ligante—l-arginina e l-glutamato mononatriate—esseva administrate a 11 patientes con encephalopathia hepatic associate con cirrhosis de Laennec. Ben que il esseva constatate que le nivellos de ammonium arterial esseva reducite significativemente in omne casos, solmente 2 del patientes se meliorava sufficientemente pro esser dimittite ab le hospital. In despecto de un leve augmento del total consumption cerebral de oxygeno e del fluxo de sanguine cerebral, nulle correlation esseva trovate inter iste valores, le nivellos arterial de ammonium, e le stato clinic del patientes. Es reiterate que ammoniaco de origine endogene es probabilemente non le sol factor neurotoxic in le encephalopathia spontanee de patientes con morbo hepatic sever. Per consequente il non pote esser un surprisa que amino-acidos que liga ammoniaco non pote, per se o in combination, inducer grados appreciabile de melioration clinic in omne casos de encephalopathia hepatic. Tamen, iste conclusion non exclude le uso de tal amino-acidos como adjuncto in le tractamento de encephalopathia hepatic.

COBALTOUS CHLORIDE IN THE TREATMENT OF ANEMIA ASSOCIATED WITH RENAL INSUFFICIENCY AND ITS EFFECT ON THYROID FUNCTION*

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Patients with renal disease tend to develop anemia when nitrogen retention appears, regardless of the etiology of the renal lesion. The anemia is most often of the normocytic, normochromic type, occasionally macrocytic, and rarely microcytic and hypochromic (Callen and Limarzi[5]). The severity of the anemia often parallels the degree of renal insufficiency, and tends to correlate well with blood nonprotein nitrogen concentration (Callen and Limarzi[5]); the latter, however, does not imply a causal relationship. In fact, the pathogenesis of the anemia of renal failure remains obscure (Strauss and Raisz[34]), although a number of causative factors have been suggested. These include hemodilution (Brown *et al.*[4]), increased hemolysis (Emerson and Burrow[9], Loge, Lange and Moore[25]), a decrease in the life span of the red cells (Chaplin and Mollison[6], Loge, Lange and Moore[26]), and depression of red cell production by the bone marrow (Callen and Limarzi[5], Harris, Stanley and Poole[16]). Renal retention of some normally excreted toxic substance, as yet unidentified, has been offered as an explanation of the erythroid suppression. It has also been suggested that the anemia may be related to the amount of damaged renal tissue (Whipple and Robscheit-Robbins[36]), rather than to renal failure *per se*. *In vitro* studies have shown, however, that maturation of marrow normoblasts may be partially inhibited as a result of changes in the serum of anemic patients suffering from chronic renal insufficiency (Markson and Rennie[27]).

Control of the anemia of renal insufficiency is desirable, since the anemia leads to *a*) increased cardiac output (Blumgart and Altschule[2]), thereby placing an increased strain on the heart, which in renal disease often is

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already under the strain of hypertension, *b*) decreased renal clearance (Bradley and Bradley[3]) and *c*) edema (Strauss and Fox[33]). Unfortunately, therapy of the anemia of renal failure has been singularly disappointing. Usually the anemia is refractory to administration of liver extract, vitamin B_{12} and iron (Kaye[21]). Transfusions may aid in returning blood hemoglobin to its former concentration after hemorrhage in the presence of renal failure. The use of transfusions as an answer to the therapeutic problem in general, however, leaves much to be desired (Kaye[21], Strauss and Raisz[34]). In our experience the following difficulties are associated with their use: *a)* Decreased life span of the red cells makes it difficult to maintain blood hemoglobin concentrations, leading to the need for frequent transfusions. *b)* Repeated transfusions add to the risk of viral hepatitis. *c)* They also add to the risk of nonspecific reactions which may lead to anorexia, vomiting and fever, with consequent fluid deprivation tending to augment renal decompensation. *d)* Transfusions present the hazard of overloading the circulation. *e)* Lastly, on occasion we have noted diminution of renal function following transfusion, as observed by de Wardener[8] and Strauss and Raisz[34].

The refractoriness of the anemia to treatment has stimulated a search for effective therapeutic agents. One of these, cobaltous chloride, has been reported to assist in correcting the condition (Gardner[12], Weinsaft and Bernstein[35]). The rationale for the use of cobalt lies in its erythropoietic effect (Grant and Root[15]) which, as recently suggested by Goldwasser *et al.*[14], may be mediated through plasma erythropoietic hormone. One objection to its use relates to the thyroid. According to some investigators, administration of cobalt results in inhibition of thyroid function. Kriss, Carnes and Gross[23] observed hypothyroidism in one patient and thyroid hyperplasia or goiter in several of their patients treated with cobaltous chloride. Interference with radioiodine uptake from cobaltous chloride was found by Roche and Layrisse[31], and recently, Paley, Sobel and Yalow[29] and Anderson[1] showed that in some instances cobalt inhibits the organic binding of iodine by the thyroid. On the other hand, Holly[17] and Jaimet and Thode[19] reported that administration of cobalt to anemic patients had no measurable effect on the thyroid.

In the present study cobaltous chloride was given at the dose level commonly used for the treatment of the anemia of renal insufficiency with the objective of evaluating its effect on hematologic values and, more particularly, on thyroid function.

Materials and Methods. Cobaltous chloride was administered to 12 anemic patients, aged 21 to 69 years, who had renal lesions of varying etiology. The data on the patients are summarized in Table 1. The diagnosis was chronic glomerulonephritis in 6 patients, polycystic disease of the kidneys in 2, suppressed chronic pyelonephritis in 2, hydronephrosis of a single kidney with severe active infection in one, and diabetic nephropathy of a single kidney in one. These patients had varying degrees of renal insufficiency and azotemia, except for one patient (Uh) who had no renal impairment and another (Me) who, despite previous nephrectomy and the presence of diabetic nephropathy in the remaining kidney, had questionable if any impairment. Four patients had moderate renal impairment (Groa, Ph, We, Re), and 6 had severe impairment. Four patients (Uh, Se, Mo and Ph) were not hypertensive; the rest had moderate hypertension of varying degrees. One patient (Ph) was pregnant and received cobalt following delivery while exhibiting moderate azotemia. All patients had been observed for considerable periods in the Renal Clinic. Many of them had persistent anemia, as shown by numerous blood counts preceding the count reported at the initiation of this study. All patients were in a reasonably stable physical state during the 2-month period of study. Measures directed at main-

taining electrolyte and acid-base balance, as previously described (Hopper, Bolomey and Wennesland[18]) were included in their regimens. Three patients (Se, Br, Fu) had received transfusions prior to initiation of cobalt therapy; the others had not.

Cobalt was administered orally in the form of enteric-coated tablets, each providing 25 mg. of pure cobaltous chloride. The dosage usually was 2 tablets given 2 to 4 times daily, providing 100 to 200 mg. per day of cobaltous chloride (Table 1). Cobalt was given for varying periods, approximating 2 months. In 4 instances, however, the patients had also received cobalt for various periods of time (as noted in Table 1) directly preceding the 2-month study period.

Routine hematologic studies were done on

TABLE 1.—SUMMARY OF DIAGNOSTIC DATA AND

Patient			Cobaltous Chloride		Therapy-Duration	Creat. Clear*	Blood NPN	Serum Creat.
Age	Sex	Diagnosis	Dose mg./day	Total mg.	days	ml./min.	mg./100 ml.	
44	Uh F	Acute pyelonephritis; renal function good	150	8,650	74	122	—	0.9
35	Me F	Diabetic nephropathy; one kidney, diabetes; renal function good	150	9,750	65	—	—	1.0
22	We M	Nephrotic state, post-streptococcal type; (receiving prednisone) moderate renal failure	150	12,000	80	52	—	2.6
64	Re F	Chronic glomerulonephritis; moderate renal failure	45 & 200	6,000	57	36	48	1.5
37	Groa M	Chronic glomerulonephritis; moderate renal insufficiency	100 & 200	13,300	70	30	76	3.4
22	Ph F	Chronic glomerulonephritis (pregnancy); moderate renal failure	100	5,600	56	26	65	3.0
40	Sa M	Polycystic renal disease; severe renal failure	100 & 200	10,300	70	18	111	7.0
69	Se M	Chronic pyelonephritis; severe renal failure	100 & 200	11,600	58	12	—	6.1
31	Gros M	Chronic glomerulonephritis; severe renal failure	100 & 200	8,400	56	12	—	9.2
37	Mo M	Chronic glomerulonephritis; severe renal failure	100 & 200	3,750	65	10	119	10.0
31	Fu M	Hydronephrosis of single kidney with nephrostomy; severe renal failure	100 & 200	4,400	37	5	282	12.0
49	Br F	Polycystic renal disease; severe renal failure	150	5,580	37	4	268	12.0

*Values corrected to 1.73 sq. meters body surface area
†Values before and after therapy period shown in column 5

venous blood obtained from each patient prior to initiation of the study and during and upon its completion. Hemoglobin determinations were performed with the Evelyn photoelectric colorimeter by the cyanmethemoglobin technique (Crosby, Munn and Furth[7]). Hematocrit determinations were carried out by the Wintrobe technique, and cell counts by the standard microscopic method.

Thyroid function studies, consisting of protein-bound iodine (PBI) and radioiodine (I_{131}) uptake determinations, were done at the beginning and end of the 2-month period. In several instances (as noted in Table 1), the initial thyroid studies were done following previous courses of cobaltous chloride. In the case of patient Se, the second PBI determination was done 4 months after cessa-

EFFECTS OF COBALTOUS CHLORIDE THERAPY

Hematologic Studies				*Thyroid Function Studies*		
Hgb† *gm./100 ml.*	*Het*† %	*RBC*† *millions c. mm.*	*Max. Retic. Response* %	*PBI*‡ *μg./100 ml.*	*I_{131} Uptake*‡ *(5 hr.)* %	*Remarks*
11.1	35	3.71	0.5	6.1	13	Had previous course of $CoCl_2$ (6,200 mg.), ending 6 months prior to present study
13.4	41	4.59		5.4	9	
12.3	38	4.17	2.2	6.2	15	
13.3	39	4.49		6.1	9	
11.4	34	3.60	1.3	5.8	8	
12.8	37	4.67		4.6	5	
10.9	31	4.00	2.3	5.0	9	Had previous course of $CoCl_2$ (2,500 mg.) during 28-day period preceding first PBI and I_{131} uptake
9.0	27	3.51		6.5	7	
11.8	37	4.23	1.3	5.6	12	
15.2	46	5.49		5.8	4	
8.7	28	3.30	1.8	—	5	
14.8	45	4.86		5.1	2	
11.1	33	3.66	1.4	4.8	13	
10.8	33	3.90		5.4	18	
10.4	30	3.42	0.7	2.7	4	Had previous course of $CoCl_2$ (26,500 mg.) during 7 months prior to present study. Initial PBI and I_{131} uptake reflect this dose. Last PBI done 4 months after cessation of $CoCl_2$
10.2	32	3.39		4.8	14	
9.9	31	3.25	0.9	4.5	6	Received an additional 12,000 mg. $CoCl_2$ during 3 months subsequent to this study. None was given during 3 months prior to necropsy
9.7	30	3.27		6.4	7	
12.0	—	4.12	1.6	5.0	4	Had previous course of $CoCl_2$ (18,200 mg.) during 3-month period prior to this study
10.6	32	3.51		4.9	4	
10.8	35	3.92	2.6	6.3	—	
5.7	19	2.04		5.0	11	
6.2	21	2.27	2.3	4.8	7	Last PBI and I_{131} uptake done 6 days after cessation of $CoCl_2$
8.0	28	2.91		4.7	8	

†Test performed at beginning and end of therapy period shown in column 5 except as noted under Remarks. Normal range: PBI = 4 to 8 μg./100 ml.; I_{131} = 8 to 29% (5-hr. uptake)

tion of cobaltous chloride, and in patient Br the last PBI and I_{131} uptake studies were done 6 days after cessation of the drug. PBI determinations were carried out according to a modification of the method of Salter and McKay[32]. I_{131} uptake studies were made with Geiger and scintillation counters 5 hours after administration of a tracer dose of approximately 50 microcuries of I_{131}. The patients were examined for any clinical evidence of thyroid enlargement or hypothyroidism at frequent intervals during and after treatment.

Results (summarized in Table 1). HEMATOLOGIC EFFECTS. The effect of cobalt on the anemia of these patients was variable. In 3 patients (Se, Gros, Sa) no increase in hemoglobin concentration and no significant change in hematocrits, red cell counts, or mean corpuscular hemoglobin concentration values occurred during therapy. In 3 patients (Re, Mo, Fu) hemoglobin, red cell and hematocrit values decreased, but no change took place in mean corpuscular hemoglobin concentration. Creatinine clearance was seriously impaired in 2 of these patients (Mo, Fu). In the remaining 6, hematologic values increased, on an average of 2.6 gm. of hemoglobin per 100 ml., 7.1% hematocrit, and 0.94 million red cells per c.mm. In the majority of these patients the increase in hemoglobin concentration and red cell count occurred within one month, and maximal increases were obtained in 5 to 14 weeks (average, 9½ weeks). Mean corpuscular hemoglobin concentration was increased in only one case (Groa), from a value of 31 to 41 (Fig. 1). This patient received 1.2 gm. daily of ferrous sulfate during a control period in which hemoglobin concentration fell. He later became unresponsive to cobalt when his creatinine clearance fell to 13 ml. per minute.

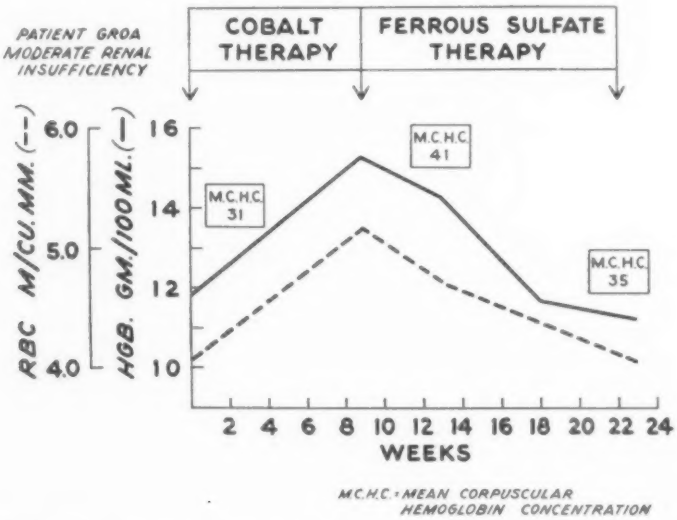

Fig. 1.—Effect of alternate periods of cobalt and iron therapy on the anemia associated with renal insufficiency.

Reticulocyte response was never pronounced, and appeared as great in patients whose hemoglobin values showed no change as in those whose hemoglobin increased. Total and differential leukocyte counts showed no

significant alterations in the total group, even though patients Se and Fu had active infections associated with renal insufficiency.

THYROID FUNCTION. As shown in Table 1, no significant decrease occurred in the serum PBI concentrations of 7 patients in whom the PBI was determined before and after 2 months of treatment. In 2 patients (Mo and Re) who received cobalt for 3 months and 1 month respectively prior to the 2-month study period, two PBI determinations at 2-month intervals during treatment showed no remarkable changes. In one patient (Se) treated for a total of 9 months, the PBI was 2.7 μg. per 100 ml. of blood after 6 months of treatment and 4.8 μg. per 100 ml., 4 months after cobaltous chloride had been discontinued. In one patient no initial value was obtained, and in 3 decreases of questionable significance occurred.

Of 7 patients in whom the 5-hour thyroid uptake of I_{131} was determined before and after 3 months of cobaltous chloride therapy, 5 showed moderate depression of I_{131} uptake, compared to pre-treatment values. The I_{131} uptake was low in 2 of 3 patients studied after therapy was initiated. In one of these cases (Se), the I_{131} uptake was within the normal range 3 days after cessation of cobaltous chloride. In one patient (Fu) the figures are incomplete.

None of the patients, including Se, developed a goiter or clinical symptoms or signs of hypothyroidism. Necropsies performed on 2 patients (Gros and Fu), who died of renal failure 3 months and 76 days respectively after cessation of cobaltous chloride therapy, showed no evidence of thyroid hyperplasia.

In addition, cobalt had no observable adverse effect on the underlying renal disorder in these patients. There was no instance of coronary occlusion attributable to cobalt therapy as reported by others (Gardner[12]).

Discussion. The results of this study indicate that treatment with cobaltous chloride is not always capable of overcoming the "anti-stimulus" to erythropoiesis imposed by renal failure. It is our impression, however, that administration of cobalt often stabilized the anemia at a satisfactory level, making the need for transfusions less frequent.

Under the time-dosage schedule used in this study, thyroid function was not altered significantly. Moderate reduction in I_{131} uptake occurred in some of our cases, but subsided rapidly upon withdrawal of cobalt. No significant changes in PBI were observed (with one exception, patient Se). No instance of hypothyroidism or goiter was encountered in our patients.

As previously suggested (Hopper, Bolomey and Wennesland[18]), treatment of the anemia of renal insufficiency should be pursued along multiple fronts. Relief of renal decompensation, in particular, is likely to result in improvement. Since cobaltous chloride is of benefit in some patients and does not appear to have a permanently adverse effect on thyroid function, we are inclined to use it as an additional measure for the treatment of the anemia of renal failure. It has not been found necessary to provide concomitant substitution therapy with thyroid.

Summary. The effects of cobaltous chloride on the anemia of chronic renal disease was studied in 12 patients. Thyroid function was evaluated before and upon completion of therapy in 9 patients and during therapy in 3.

Six of the 12 patients showed hematologic improvement, with an average increase of 2.6 gm. of hemoglobin per 100 ml. of blood. The status of the renal disease apparently was unaffected by the medication. No patient devel-

oped signs of clinical hypothyroidism or thyroid hyperplasia, and no remarkable changes in the serum protein-bound iodine concentration were observed. A moderate reduction in radioiodine uptake by the thyroid was noted in some cases, but this effect disappeared rapidly upon cessation of cobalt therapy.

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SUMMARIO IN INTERLINGUA

Chloruro Cobaltose in le Tractamento de Anemia Associate con Insufficientia Renal—Su Effecto Super le Function Thyroide

Le effecto de un tractamento con chloruro cobaltose super le anemia associate con insufficientia renal esseva studiate in 12 patientes. Le concentration de hemoglobina e le numeration erythrocytic esseva afficite favorabilemente in certe casos. Le function thyroide esseva mesurate per determinationes de iodo ligate a proteina e del acceptation de iodo radioactive. Iste ultime esseva reducite moderate- e temporarimente in alicunes del casos, sed le iodo ligate a proteina non esseva afficite notabilemente.

THE DIAGNOSIS OF TRAUMATIC MITRAL REGURGITATION BY CARDIAC VENTRICULOGRAPHY

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The development of significant and dynamic mitral regurgitation following mitral commissurotomy is not rare. In a recent comprehensive review of the results of mitral commissurotomy from 37 clinics, 2.1% of 10,000 cases analyzed developed this complication (Am. Coll. Chest Phys.[1]). Milder forms occur more commonly.

The frequency of this lesion emphasizes the importance of adequate diagnostic procedures for its detection. The present communication deals with a radiologic opacification procedure, cardiac ventriculography-left, which was employed successfully in the diagnosis of 4 cases of traumatic mitral regurgitation following commissurotomy for tight mitral stenosis.

Methods and Materials. The procedure of cardiac ventriculography has been previously described by Lehman, Musser and Lykens[3]. It involves subxiphoid needle puncture of the left ventricle, with rapid injection of highly concentrated radiopaque medium to completely opacify the left ventricular chamber.

Details of pressure and electrocardiographic monitoring, radiopaque injection and filming have also been reported (Lehman, Musser and Lykens[3]).

Regurgitant opacification of the left atrium is observed in the presence of significant dynamic mitral insufficiency. In the absence of mitral valvular insufficiency, there is no appreciable reflux into the left atrium (Uricchio *et al.*[5]).

Case Reports. CASE 1. S.L., a 37-year-old white woman, was well until December, 1956, when she developed pulmonary edema. At that time the diagnosis of mitral stenosis combined with a minor degree of aortic stenosis and regurgitation was established clin-

ically. Cardiac auscultation revealed a normal sinus rhythm, a mid-late apical diastolic murmur, a sharp mitral first sound, and an accentuated P_2. A grade 1 aortic systolic murmur was present in association with a normal A_2. An early diastolic murmur was present along the left sternal border. Blood pressure was 122/68.

After a preliminary diagnostic survey including left heart catheterization was completed, mitral commissurotomy was performed on January 9, 1957. No mitral regurgitation was noted at surgery. The valve was fibrotic and free of calcium. A tight mitral stenosis was present.

Postoperatively, the patient was troubled by constant fatigue, dyspnea, orthopnea and cough. Limitation of activity and a strict medical regimen were unsuccessful in controlling her symptoms. Cardiac auscultation demonstrated the same auscultatory events at the aortic area, but a grade 4 systolic murmur was now noted over the apex. No apical mid-diastolic murmurs were audible.

Cardiac ventriculography-left, performed on June 30, 1958, demonstrated a 3 plus reflux opacification of the left atrium (Fig. 1).

Surgical reconstruction of the mitral valve was carried out on August 1, 1958, utilizing complete circulatory bypass. Marked mitral regurgitation was present and a tear in the septal leaflet was detected in the region of the anterior commissure. The technique of this operation is to be reported (Nichols, Sparger and Uricchio[4]).

CASE 2. B.N., a 40-year-old white woman gave a history of a transient hemiplegia 5 years before admission to Hahnemann Hospital on December 12, 1956. Since then, she has had exertional dyspnea, fatigue and epigastric fullness. More recently, orthopnea appeared. Cardiac auscultation at the time of entry revealed the presence of a sharp mitral first sound, an apical mid-late diastolic murmur, an opening snap, and an accentuated P_2. A grade 2 systolic murmur was heard over the tricuspid area. Atrial fibrillation was present. Blood pressure was 126/70.

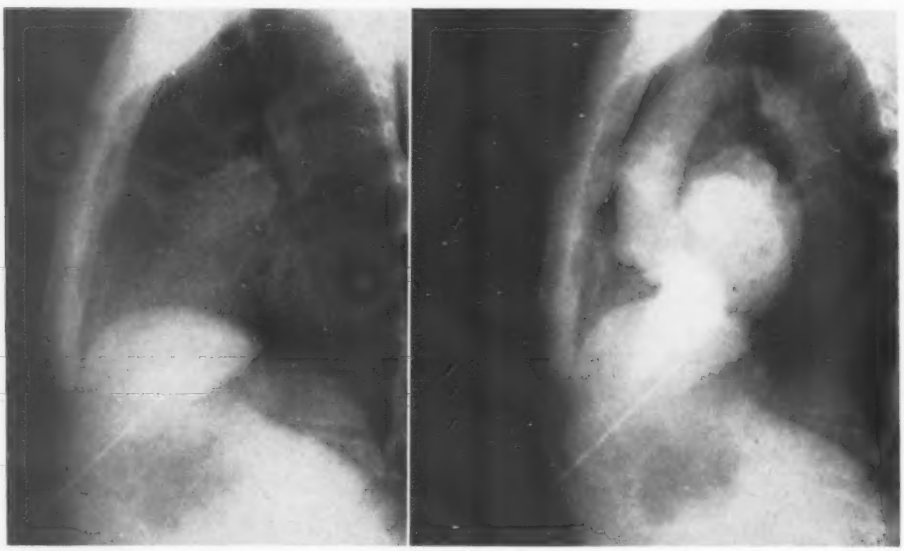

Fig. 1.—Cardiac ventriculography-left. Patient S.L. Injection of a contrast medium into the left ventricle leads to immediate reflux opacification of the left atrium, indicating the presence of serious mitral regurgitation.

A mitral commissurotomy was performed on December 20, 1956. No mitral regurgitation was noted. A tight mitral stenosis was present. The valve was fibrotic and free of calcium.

Postoperatively, the patient was troubled initially by the manifestations of the postcommissurotomy syndrome. Gradually, fatigue and progressive dyspnea developed, followed by evidence of right heart failure. Strict medical therapy failed to control the deterioration.

Cardiac auscultation revealed the presence of a grade 3 apical systolic murmur and atrial fibrillation. M_1 was normal and an opening snap could not be heard. P_2 was markedly accentuated.

Cardiac ventriculography-left performed on December 3, 1957, demonstrated the presence of significant reflux opacification of the left atrium (3 plus).

Open reconstruction of the mitral valve was performed on August 28, 1958. The valve was incompetent posteriorly, with a tear into the septal leaflet. A satisfactory result was accomplished, and subsequent cardiac ventriculography on September 9, 1958, was negative for evidence of mitral insufficiency.

CASE 3. E.B., a 23-year-old white woman experienced dyspnea and fatigue for 2 years, prior to her admission to Hahnemann Hospital on June 5, 1955, for mitral commissurotomy. Cardiac auscultation at the time of entry revealed the presence of a normal sinus rhythm, a grade 1 aortic systolic and diastolic murmur, an apical mid-late diastolic murmur, an opening snap, a sharp M_1, and an accentuated P_2. The blood pressure was 138/70.

Mitral commissurotomy was performed on June 14, 1955. A tight mitral stenosis without regurgitation was noted.

The patient progressed satisfactorily until the summer of 1958, when dyspnea and fatigue returned and she was unable to engage in average activity. Cardiac auscultation revealed similar findings at the base of the heart, but a loud apical systolic murmur was now present. The rhythm was regular.

Cardiac ventriculography-left, performed on November 15, 1958, demonstrated marked reflux opacification of the left atrium (3 plus) (Fig. 2). Reconstruction of the incompetent mitral valve, utilizing complete circulatory bypass, was carried out successfully on February 12, 1959. At surgery, a tear was found in the septal leaflet.

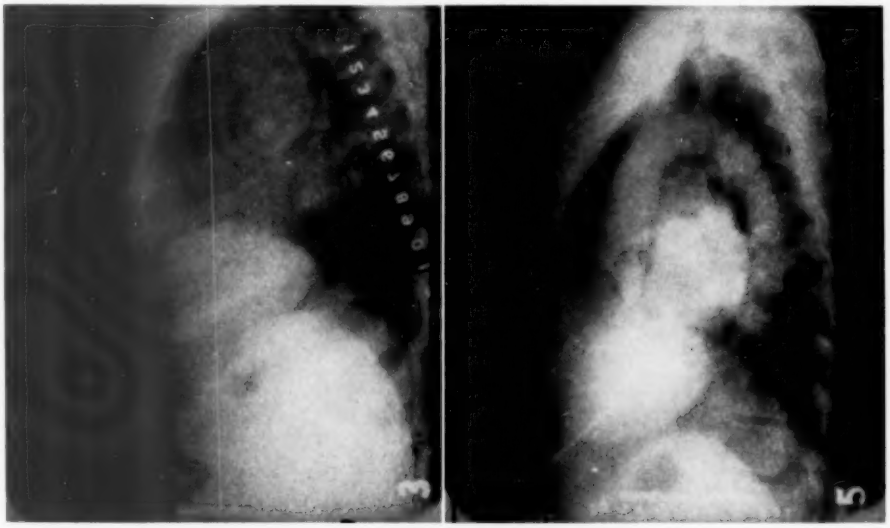

Fig. 2.—Cardiac ventriculography-left. Patient E.B. (*a*). Lead numerals are affixed to the chest wall as an aid in determining the direction of the needle pass into the left ventricle (*b*). The needle pass is made swiftly under electrocardiographic and manometric monitoring into the left ventricle. Contrast medium is injected and, in this case, it flows across the incompetent mitral valve into the left atrium.

CASE 4. B.P., a 23-year-old white woman, complained of fatigue and slight limitation of activity at the time of her hospital survey in November, 1957. Cardiac auscultation at that time revealed the presence of an apical presystolic murmur, a sharp M_1, an opening snap, and an accentuated P_2. There was a normal sinus rhythm. The blood pressure was 110/70. Mitral commissurotomy was carried out on November 15, 1958. The valves were fibrotic and free of calcium. No regurgi-

tation was present, and a tight mitral stenosis was encountered.

Postoperatively the patient had numerous bouts of pulmonary edema, with evidence of advanced right heart failure. Cardiac auscultation revealed only a loud, grade 4 apical systolic murmur. A normal sinus rhythm was still present. No diastolic murmurs were heard.

Fig. 3.—Cardiac ventriculography-left. Patient B.P. The left ventricle, left atrium, coronary vessels, and aorta were opacified within 3 seconds following the injection of contrast material. The test was diagnostic of traumatic mitral regurgitation.

Cardiac ventriculography-left was performed on December 12, 1958, and revealed marked reflux opacification of the left atrium (Fig. 3).

Open reconstruction of the mitral valve was carried out successfully on December 15, 1958. Marked (4 plus) regurgitation was noted at surgery and some of the chordal supports to the septal leaflet were found to be detached. A successful result was obtained.

Discussion. Serious grades of mitral regurgitation following mitral commissurotomy must be differentiated from the benign forms of postoperative mitral incompetence. The former is a lethal disease which develops from surgical tears into the leaflets, the annulus fibrosus or the supporting chordae tendinae. It leads to a marked increase in the work of the left ventricle. The effective cardiac output invariably falls. In addition, pulmonary hypertension may develop in the presence of progressive vascular changes in the arterioles and medium-sized arteries. The latter cycle, accentuated in the presence of a small left atrium, may pave the way to the development of right ventricular failure (Bentivoglio, Uricchio and Likoff[2]).

The other form of postoperative mitral regurgitation is mild and innocuous. It does not interfere with the favorable response following mitral commissurotomy, nor is it responsible for any detrimental hemodynamic effects. Actually, its appearance at surgery indicates that the ideal termination point has been reached and that further extension of the commissural cleavage line is undesirable.

Both types of postoperative mitral regurgitation produce identical auscultatory events at the apex. A loud apical systolic murmur, a dull or normal mitral first sound, and a protodiastolic gallop are common to both syndromes, albeit the findings are more striking in those with serious degrees of traumatic mitral regurgitation.

A previous report by Uricchio and associates[5] demonstrated that direct needle puncture opacification of the left ventricle has considerable reliability in the assessment of mitral valve leak. In that investigation, 42 cases of isolated rheumatic mitral valve disease were studied by this technique prior to cardiac surgery. Twenty-eight cases demonstrated two plus or greater reflux opacification of the left atrium on cardiac ventriculography and all had dynamic mitral regurgitation of an advanced degree at operation. In each instance, it was necessary to perform a surgical procedure for correction of the mitral incompetence.

Nine cases in the special series had no evidence of opacification of the left atrium on cardiac ventriculography and all had a tight mitral stenosis. Five patients had one plus reflux opacification of the left atrium. Only 3 of this latter group had a minor degree of central regurgitation at surgery which disappeared almost completely following mobilization of the stenotic valve. No evidence of incompetence was observed at operation in the remaining 2.

It is reasonable to conclude, therefore, that cardiac ventriculography-left will permit the clear cut separation of the two types of postoperative mitral incompetence. In the benign form of which we have studied several, direct needle puncture opacification of the left ventricle does not lead to significant reflux opacification of the left atrium (2 plus or greater).

On the other hand, as the present report demonstrates, serious mitral regurgitation is associated with marked reflux opacification of the left atrium on cardiac ventriculography-left.

The procedure is reasonably safe if proper precautions are taken with regard to placement of the needle within the heart chamber (Lehman, Musser and Lykens[3]). These factors have been considered in detail in other communications (Bentivoglio Uricchio and Likoff[2], Lehman, Musser and Lykens[3]).

The present report suggests another valuable application of cardiac ventriculography and emphasizes its importance following mitral commissurotomy if the patient is symptomatic and traumatic, mitral regurgitation is suspected clinically.

Summary. Cardiac ventriculography-left (direct transthoracic needle puncture opacification of the left ventricle) was employed successfully in the diagnosis of 4 cases of traumatic mitral regurgitation which resulted from previous mitral commissurotomy.

All 4 cases had a greater than one plus reflux opacification of the left atrium and everyone was demonstrated at surgery to have an advanced degree of mitral regurgitation.

Cardiac ventriculography-left provides a reliable technique for the differentiation of serious grades of mitral regurgitation following mitral commissurotomy from the benign forms of postoperative mitral incompetence.

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SUMMARIO IN INTERLINGUA

Le Diagnose de Traumatic Regurgitation Mitral, Effectuate per Ventriculographia Cardiac

Cardioventriculographia sinistre (opacification del ventriculo sinistre per acupunctura transthoracic directe) esseva usate a bon successo in le diagnose de 4 casos de traumatic regurgitation mitral, occurrente como resultato de un previe commissurotomia mitral.

Omne le 4 casos habeva un opacification de refluxo in excesso de 1+ in le atrio sinistre. In omnes le intervention chirurgic produceva le prova de un grado avantiate de regurgitation mitral.

Cardioventriculographia sinistre provide un technica fidel pro le differentiation inter (1) serie grados de regurgitation mitral post commissurotomia mitral e (2) formas benigne de postoperatori incompetentia mitral.

SUMMARIO IN INTERLINGUA

(See page 55 for original article)

Un Nove Agente Anorectic, Non Affin A Amphetamina

Un serie de 178 patientes esseva tractate, con le objectivo de reducer lor pesos, per medio del nove anorectico a action prolongate, 2-phenyl-tertiobutylamino-resina (Ionamina). Le experientia in le uso de Ionamina durante un total de 2587 dies/patiente esseva evalutate clinicamente. Un perdita de peso de approximativemente 0,25 libra per patiente per die esseeva effectuate. Iste nove droga es efficace in le suppression de appetito, e illo ha un significativemente plus basse incidentia de effectos lateral que occurre in le uso de therapeuticamente equivalente doses de amphetamina. Individuos in qui le effecto de altere anorecticos se habeva horizontalisate, respondeva satisfactorimente a iste agente.

NEUROLOGICAL SYMPTOMS AND LESIONS OCCURRING IN THE COURSE OF REITER'S DISEASE*

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Reiter's disease as seen in the British Isles is a disorder characterized by venereally transmitted nonspecific urogenital infection, and polyarthritis of a recurrent and relapsing nature. Conjunctivitis, or iritis, keratoderma blenorrhagica and lesions of the mucosae are frequent accompanying manifestations but their presence is not essential in making the diagnosis. On the continent of Europe this disease is reported most commonly in association with diarrhea and dysentery, nonspecific urethritis being present in almost all cases. There is no evidence to prove that the dysenteric and venereally transmitted forms differ. The cause remains undiscovered, but there seems little doubt that the disease process is of an infective nature.

Before the introduction of penicillin, gonococcal urethritis was considered by many to be the causative infection. This error led to the slow recognition of the identity of Reiter's disease, and occasioned much confusion in the literature, many examples of the condition being reported as "gonococcal polyarthritis." It is now generally accepted that gonococcal urethritis plays no part either in the genesis or the course of Reiter's disease, and that its presence is coincidental.

It is clear from the literature that almost all the body systems can be involved. The least commonly affected seems to be the nervous system, and it is in this context that the following 3 cases, all seen in the same clinic in a period of 18 months, are considered to be of interest.

Case Reports. Case 1. The patient, a married man aged 49, developed gonococcal urethritis one week after a homosexual exposure on Feb. 1, 1957. One week later he developed bilateral conjunctivitis, keratodermic papules on the glans penis, and arthritis affecting the left shoulder, both knees and the left ankle. The past history revealed that he had had a "slipped disc" 7 months before, cystitis 3 years before, and some form of "nervous trouble" which he refused to discuss.

He was admitted to the hospital on Feb. 22, 1957, and a detailed physical examination revealed no abnormal findings other than those recorded. The blood pressure was 115/70 mm. Hg. The urine contained no albumin or sugar.

The erythrocyte sedimentation rate was 66 mm. per hour (Westergren). The hemoglobin was 97%, and white blood cells numbered 10,000 per c.mm., with 69% polymorphonuclear leukocytes, 23% lymphocytes, 6% monocytes, and 2% eosinophils. The following were found to be negative or within physiological limits: serological tests for syphilis, Rose's test, agglutinations for dysenteric organisms, serum proteins and A/G ratio, blood uric acid, chest roentgenogram and electrocardiogram. Fluid aspirated from

*This work was carried out under the aegis of the Medical Research Council Working Party on Non-Specific Urethritis, with the aid of a grant from the United States Public Health Service.

a knee joint was sterile on culture. Biopsy was performed on a penile lesion and the microscopical findings were compatible with those in keratoderma blenorrhagica.

He was treated with procaine penicillin 600,000 units intramuscularly on the day of admission, and on the fifth day in hospital he began a 5 day course of tetracycline hydrochloride 500 mg., q.i.d., for the treatment of a profuse nongonococcal urethral discharge which had become evident after the penicillin therapy.

For a period of 25 days, between February 22 and March 18, 1957, he received phenylbutazone 200 mg., b.d., which gave satisfactory relief from his joint pains. In the earlier part of this period he ran a low grade fever in the evenings, other joints were transiently affected, the blood sedimentation rate remained raised, and the white cell count remained in the region of 10,000 cells per c.mm. Later he began to gain weight and his conjunctivitis subsided, but he found difficulty in sleeping and a bromide mixture was prescribed. Re-examination from time to time revealed no evidence of involvement of other systems.

On March 16, his conjunctivitis recurred and his morning temperature rose to 100° F. Two days later he complained of a dry throat. There were no mucosal or skin lesions, nonetheless the phenylbutazone was discontinued as a precautionary measure and blood was taken for a white cell count. During the night he was reported as being mentally confused and at 9.30 a.m. on March 19 he was found to be suffering from paranoid delusions. An examination of the nervous system revealed no abnormal physical findings, the fundi, blood pressure and urine were normal, the blood sugar and blood urea were normal and the blood bromide content was less than 25 mg. per 100 ml. The blood count of the previous day was as follows: Leukocytes numbered 2,800 per c.mm., with 52% neutrophils, 28% lymphocytes, 7% monocytes, and 11% eosinophils. By 10.15 a.m. he was mute and catatonic and at 11.30 a.m. he gave a loud cry and had a major epileptiform convulsion with tongue biting and incontinence. Examination of the cerebrospinal fluid (C.S.F.) was performed, the fluid being at normal pressure and crystal clear until he momentarily escaped restraint when it became tinged with blood. There was a free rise and fall on jugular compression. The findings were as follows: Protein 250 mg. per 100 ml., white cells 29 per c.mm. (estimated excess in relation to blood contamination), chlorides 686 mg. per 100 ml., sugar 50 mg. per 100 ml., Wassermann reaction negative, culture sterile. Throughout the day he remained deeply unconscious and his temperature rose to 101° F. By evening he was responsive to pain, there was photophobia, neck rigidity, marked congestion of the retinal vessels and equal swelling of both optic discs. The right plantar response was extensor. The blood pressure was 110/70 mm. Hg. On March 20, purpuric lesions were detected on the hard palate, the anterior axillary folds and the palmar surfaces of the fingers. The white cell count was 4,800 cells per c.mm., with 57% neutrophils, 40% lymphocytes, 3% monocytes, and 0% eosinophils. The platelet count was normal. He regained consciousness in the early hours of March 21: there were then no abnormal signs in the central nervous system, he was drowsy but his mental state was otherwise normal, the optic neuritis had subsided and his conjunctivitis was less.

From then onwards the leukocyte count rose slowly, reaching 7,900 cells per c.mm. by April 3. Cerebrospinal fluid examinations on later occasions showed a gradual fall in the protein content, the findings in the last examination being, a clear fluid under normal pressure, cells 8 per c.mm., protein 60 mg. per 100 ml. and the culture sterile.

His arthritis had not undergone any notable alterations during this period and later with all drug therapy withdrawn, the components of his Reiter's disease slowly improved. He was discharged for convalescence on April 15, 1957. Attempts to obtain details from his family about his earlier mental trouble met with no success.

He has since been seen as an outpatient. There has been a recurrence of his polyarthritis, but there have been no further neurological manifestations.

CASE 2. This patient, a married man aged 40, contracted gonococcal urethritis in 1938 for which he was treated with irrigations. In 1945, whilst in the Navy, he developed "gonococcal arthritis" and was ill for about 6 months, the joints of the feet and lower limbs being mainly affected.

Nine days before the present admission to the hospital, he developed a low back pain which was made worse by bending and caused him to wake at night when he turned over in bed. The next day this pain became more intense, he felt generally off color, and complained of sore eyes and pain in the region of the right heel. He then experienced some terminal dysuria and frequency but saw no urethral discharge.

Examination on admission showed a fit

looking man in some pain. T. 99.8° F., P. 80. There was a fairly severe bilateral conjunctivitis and the hard palate showed shallow erosions of the mucous membranes. The penis was uncircumcised and retraction of a tight prepuce showed the presence of several plaques of circinate balanitis. There was a purulent urethral discharge. No evidence of arthritis was found but the right tendo-achilles was swollen and painful and there was well-marked tenderness on pressure over the interspinous ligaments in the region of the first lumbar vertebra. Spinal movements were full but flexion produced some pain in the lumbar region. Straight leg raising was full, painless and equal on the 2 sides, and tests for the presence of disease of the sacro-iliac joints were negative.

Two days after admission he began to complain of severe pain in the region of both shoulders but particularly the left. The pain was aching in nature, worse at night and on the left side spread down to the elbow. After a few days he noted that both arms were becoming weak especially the left one. This weakness rapidly progressed and he was soon unable to fasten buttons with the left hand or to lift his left arm above shoulder level to brush his hair. At the same time an eruption of miliary keratoderma blenorrhagica appeared on the anterior surface of the chest and the left arm, and a cluster of rupial keratodermic lesions appeared on the sacral region. Shortly before the eruption evolved, he developed arthritis of the left ankle and knee, the right mid-tarsal and several metatarso-phalangeal joints.

Physical examination at this stage showed, besides evidence of arthritis, gross weakness and gross wasting of the left deltoid, biceps and triceps muscles and, to a lesser degree, some weakness of all muscles innervated from the 5th cervical segment. There was a little weakness of the right deltoid and triceps but no obvious wasting. The tendon jerks were brisk and equal on both sides and no sensory changes could be detected. The weakness and wasting progressed slowly on the left side for about 10 days, after which time a gradual improvement took place. Following the institution of active physiotherapy power began to return to the affected muscles, but the wasting was still severe when he was discharged from hospital 7 weeks later, and still appreciable when he was seen as an outpatient 3 months later.

Relief from joint pains was achieved by giving 100 mg. phenylbutazone, t.i.d., and the joint swelling had completely subsided on his discharge.

The urethritis persisted throughout his hospital stay in spite of treatment with tetracycline hydrochloride by mouth and streptomycin by intramuscular injection.

A Gram-stained smear of the urethral discharge showed many pus cells but no gonococci. No Neisseria were grown in culture and the gonococcal complement fixation test was negative. The sedimentation rate was 80 mm. per hour (Westergren), falling to 30 mm. per hour on discharge. Agglutination reactions for dysenteric organisms were negative in all dilutions and roentgenograms of the sacro-iliac and affected joints and of the cervical spine showed no abnormality. The electrocardiographic tracing was physiological. At lumbar puncture, carried out 10 days after the onset of muscle wasting, the C.S.F. was clear, at normal pressure, and with a free rise and fall on jugular compression. The cell count was less than 1 per c.mm., and the protein was 30 mg. per 100 ml. Electrodiagnosis was carried out and reported on as follows by Dr. L. Steinberg: "Stimulation of the brachial plexus caused contraction of the lateral head of the biceps only. Intensity duration curves in the left deltoid, biceps and triceps were normal. Electromyograph: the left deltoid showed some fibrillation at rest. Reinforcement was normal. Interference pattern was good. Units were mainly long duration polyphasics. Conclusion: a peripheral neuropathy. The curves were normal probably as the lesion was of only 14 days duration."

CASE 3. This patient, a married man aged 24, worked as a lorry driver. One week after sexual exposure with a casual acquaintance he developed gonococcal urethritis for which he received treatment with 1.2 mega units of procaine penicillin intramuscularly. His discharge decreased in amount but did not stop and 4 days later he developed dysuria, frequency and terminal hematuria. A Gram-stained smear of the urethral discharge showed many pus cells, but no gonococci could be found and none were isolated in culture. The next day his eyes were red and sore and in the evening he began to experience a sharp tearing pain in the region of the left groin which appeared to radiate round the thigh from as far back as the posterior superior iliac spine. The pain was present only in short spells lasting a few seconds or minutes, and was brought on by coughing or sudden movement such as sitting up from a prone position or turning over in bed.

The patient gave no past history of venereal disease or of any rheumatic disorder.

Examination showed a young man in some severe pain. T. 98.4° F., P. 70. There was bilateral conjunctivitis, and erosions were present on the mucosae of both the hard palate and the cheeks. The penis was uncircumcised and the glans penis showed a severe circinate balanitis. There was a purulent urethral discharge. Straight leg raising on the left side was limited to 30 degrees, apparently by pain, and there was a considerably wavy tremor. Spinal movements were full and painless, tests for evidence of sacro-iliac joint disease were negative, and there was no evidence of arthritis. There was an acutely tender area one inch to the left of the midline at the level of the sixth dorsal spinous process. Advice was obtained from a neurologist, who gave as his opinion that the patient's symptoms suggested a radiculitis, but that the only physical signs were of functional weakness and tremor of the lower limbs. A lumbar puncture was carried out and findings in the C.S.F. were entirely normal. During the next 4 days the patient's symptoms rapidly improved though he then developed arthritis of both mid-tarsal joints, the left shoulder, the 2nd and 3rd metacarpal and nearly all the metatarso-phalangeal joints. Keratodermic lesions appeared on the soles of the feet. Two weeks after admission he complained of severe "crushing" pain in the medial side of the left thigh. It was quite unlike the original pain experienced in the groin. Examination revealed tenderness and swelling at the insertion of the tendon of the adductor longus muscle. It was concluded that this was a tendinitis; it proved to be of short duration and the pain was rapidly relieved with subcutaneous pethidine.

Phenylbutazone was ineffective in relieving the pain of his arthritis. Oral Prednisone was substituted and there was a considerable subjective improvement on a maintenance dose of 15 mg. given twice daily. The patient eventually took his own discharge against medical advice, to attend to urgent personal affairs!

Discussion. Most previous reports of neurological disturbances occurring in association with Reiter's disease are from the continent of Europe and deal mainly with those cases in which the disease is related to diarrhea or dysentery. Schittenhelm and Schlecht[6] (1918) analysing 106 such cases, found one with trigeminal neuralgia, 3 with sciatica and one with facial palsy. In a group of 34 cases, none of whom had any history of an intestinal disorder, one patient had "intercostal neuralgia" and one "torticollis." Walther[7] (1941) made brief reference to trigeminal neuralgia, sciatica and polyneuritis occurring in association with the dysenteric form. Wilke[8] (1943) noted polyneuritis of 2 main types occurring with Reiter's disease. In one variety the nerves to the shoulder and pelvic girdle muscles were chiefly affected and few sensory changes were present, in the other the picture was of multiple peripheral neuritis. He noted an increase in the protein content of the cerebrospinal fluid in several cases though the cell counts were usually normal or only slightly increased. Zewi[9] (1947) described 2 patients who developed optic neuritis. From the case histories it is clear that both had the dysenteric form of the disease. Graby, Hosotte and Armand[2] (1949) recorded a patient who developed polyneuritis with foot drop during an attack of Reiter's disease which had followed amebic dysentery. The protein content of the cerebrospinal fluid was 90 mg. per 100 ml. and the cell count 1 per c.mm. Lafon, Pages, Roux, Temple and Minvielle[3] (1955) reported the case of a 44-year-old man with idiopathic epilepsy who developed a right sided hemiplegia in the course of an attack of Reiter's disease with iritis. The cerebrospinal fluid was normal, ventriculograms were normal and no other neurological changes were present. The hemiplegia improved spontaneously in 2 weeks. There was no preceding history of dysentery. Csonka[1] (1958) described the case of a man of 29 who had developed neurological manifestations in association with 3 out of 7 attacks of venereally acquired Reiter's disease. These manifestations included retention of urine, nystagmus, facial and sixth nerve palsies, sensory

disturbances in the trigeminal nerve and alterations in the limb reflexes. The cerebrospinal fluid was examined in the course of one attack and was found to be normal.

In case 1 the patient sustained a short lived attack of meningoencephalitis which was followed by complete and spontaneous recovery. Three explanations can be advanced. Firstly that his symptoms were caused by phenylbutazone. In support of this was the fall in the white cell count and the development of purpuric lesions. However, no such toxic effect of phenylbutazone has been previously reported or has come to the notice of two prominent manufacturers of the drug, and the dosage was modest. Purpura in Reiter's disease has been reported by Makari[4] (1950) and we have seen it localized to the region of severely affected joints in 2 patients. Depression of the total white cell count has been noted by Walther[7] (1941) and Paronen[5] (1948). Secondly, that his symptoms were caused by infection with one of the many viruses known to cause meningo-encephalitis. The onset with fever and sore throat are in favor of such a cause, but no virus studies were carried out. Thirdly, that the meningo-encephalitis was caused by the agent responsible for Reiter's disease. In this connection it is noted again that the neurological symptoms appeared to begin shortly after the recurrence of his conjunctivitis.

In case 2 the connection with Reiter's disease is perhaps stronger as the association has been noted several times before. Isolated attacks of neuritis of unknown but possibly infective origin are well recognized and the fifth cervical segment is most commonly affected, as it was in this case. Whilst the occurrence of such an attack with Reiter's disease could be coincidental, it seems rather unlikely.

In case 3 the patient experienced attacks of root pain but no physical signs indicating disease of the central nervous system were found and the cerebrospinal fluid was normal. The symptoms could have been produced by pressure on the posterior root of the first lumbar nerve on the left side and perhaps the commonest cause of such pressure is a herniated or prolapsed intervertebral disc. However, the mode of presentation, course, radiological and physical findings made this explanation, though possible, very unlikely. Areas of local tenderness often described as "myositis" or "fascitis" are very commonly seen in Reiter's disease, especially in the paravertebral region. Such local plaques of inflammation rarely persist for more than a week and possibly such a lesion was responsible for the root pain experienced in case 3.

Summary. 1. The literature relating to neurological involvement in Reiter's disease is briefly reviewed. 2. One case of "shoulder girdle" neuritis, one of meningo-encephalitis and one of a patient with symptoms of root pain, each occurring in association with an attack of Reiter's disease, are described.

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SUMMARIO IN INTERLINGUA

Symptomas e Lesiones Neurologic Occurrente in le Curso de Morbo de Reiter

1. Es presentate un breve revista del litteratura concernite con affectiones neurologic in morbo de Reiter. 2. Es describite un caso de neuritis del "cinctura spatular," un caso de meningo-encephalitis, e un caso con symptomas de dolores de radice, omnes occurrente in association con un attacco de morbo de Reiter.

PROGRESS
OF
MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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CLINICAL SYNDROMES OF THE GLOSSOPHARYNGEUS PRACTICAL NEUROLOGIC CONCEPTS

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THE glossopharyngeal nerve has interested anatomists since the beginning of the Christian era. In 130 A.D. Galen wrote in detailed fashion concerning this nerve. Kilian[18], of Pesth, reviewed the literature of the glossopharyngeus from the time of Galen until 1822, in which year the former's remarkable volume, devoted to the 9th cranial nerve, was published. In 1926, Dana[8] reviewed Kilian's volume and remarked on the clinical importance of the glossopharyngeus.

It is the purpose of this review to describe the current status of our clinical knowledge of the glossopharyngeus innervation, and in particular to relate the more common syndromes in which the nerve is involved, singularly or with other cranial nerves.

The glossopharyngeal nerve is of interest for physiologic reasons. One of these is its intimate functional relationship to the vagus nerve. These two nerves in their interrelationship regulate functions of a vital organ of the body, the pharynx. Through this organ passes air, saliva, fluid, and food.

The pharynx is a musculo-fascial organ which extends from the base of the skull to the cricoid cartilage, at the level of the 6th cervical vertebra. The pharynx is 12 cm. long, 5 cm. wide at the superior extremity and 2.5 cm. wide at its junction with the esophagus. The pharynx has 7 orifices: 2 openings into the Eustachian tubes, oral, laryngeal, and esophageal hiatuses, and 2 choanae.

Pharyngeal functions are concerned in: respiration, initiation of swallowing, voice resonance, articulation, taste, and ventilation of Eustachian tubes. As a lymphatic organ the pharynx is a barrier concerned with bacterial filtration and immunity. The nerves and

vessels of the pharynx may be a portal transmitting infection to other parts of the body. The first manifestations of many diseases may readily be observed in the throat. Thus the pharynx receives primary attention in the physician's examination. In many cases disease involves the innervation, frequently the abnormality is anatomic. The pain of common inflammatory processes in the pharynx, tonsil and ear is man's most ubiquitous indisposition.

The glossopharyngeal nerve arises from bulbar nuclear complexes, innervates important differential functions embodied in the pharynx and the posterior portion of the tongue as well as the chemo-and pressor-receptors of the carotid body and carotid sinus respectively. Vital carotid vascular reflexes are subserved by the glossopharyngeal nerve. After the two nerve rootlets emerge from the bulb and unite they traverse the retroolivary groove, the posterior fossa of the skull and enter the neck through the anterior compartment of the jugular fossa. In this area the glossopharyngeus, as at its origin, continues to be closely associated with the vagus and spinal accessory nerves. In the jugular fossa, the 9th cranial nerve displays two ganglia, the superior and inferior, named from their relative anatomic position.

Descending inferiorly from the lower surfaces of the petrous portion of the temporal bone, the glossopharyngeal, vagus, and spinal accessory nerves accompany the jugular vein and internal carotid artery. In their cervical path lateral to the pharyngeal wall, these nerves pass through the posterior lacerocondylar foramen and the retroparotid spaces. In the latter spaces these three bulbar nerves become associated with the hypoglossal nerve and the cervical sympathetic nerves. Clinical implications of these relationships will be mentioned later.

The glossopharyngeus functions as the sensory sentinel guarding the airway and the ear. The trigeminal nerve acts as an associate in the sensory line of defense, since it supplies pain fibers to the eye, face, nares, sinuses, cheeks, hard palate, and anterior third of the tongue. Food is perceived and given direction by the glossopharyngeal and the trigeminal nerves. The perception of foreign bodies and noxious objects on the posterior third of the tongue, or on the anterior surfaces of the epiglottis by the glossopharyngeal nerve endings results in glossopharyngeal-vagus reflex closure of the epiglottis and larynx. Thereby, food, fluid, saliva, and foreign bodies are prevented from entering the airway. Motor impulses elevate and open the pharynx for reception of fluid or food. Glossopharyngeal impulses stimulate the secretion of parotid saliva, the mechanical lubricant of swallowing. Without saliva a dry pharynx precludes the act of deglutition. In one case of acute multiple sclerosis with bulbar demyelination, parotid denervation produced sufficient dryness so that swallowing was possible only after lubrication with fluids.

An important function of the glossopharyngeus is the inhibition of respiration during the initiation of deglutition. This nerve in association with the vagus integrates the functions of speech, swallowing, and respiration. Speech is produced by expiration and is impossible during deglutition. These mechanisms must be synchronized as they cannot occur simultaneously. The glossopharyngeus is important to vital processes in general and to this synchronism in particular.

Glossopharyngeal impulses subserve ventilation of the middle ear and Eustachian tube. This is important in

three dimensional travel, either in air or water, since variation in barometric pressure is excitatory of such impulses. Without tubal and middle ear ventilation the 8th cranial nerve functions of hearing and equilibrial perception in water or in space are impaired. Eustachian tube toilet of secretions is also a function of the glossopharyngeal innervation. Failure of ventilation may occur in military flying resulting in aero-otitis media, rupture of the tympanum, vertigo, or deafness.

Paralysis of either voluntary or involuntary deglutition, or both, may cause pooling of saliva in the pharynx. This paralysis is often a part of bulbar lesions. In pooling, glossopharyngeus impulses create the distress signals of foreign fluid in the pharynx. In paralysis of the vagus nerve, the epiglottis and vocal cord reflexes fail to function. Saliva may overflow the epiglottis, pyriform recesses, and vocal cords, and enter the trachea. In such lesions of the vagus nerves neurogenic lung edema is common. Atelectasis follows.

The functions of the pharyngeal innervations or their failure in drowning are deserving of attention. Examination of the lung and bronchus, immediately following drowning, reveals that water is not often inspired. Protective obstruction of the airway is a glossopharyngeally-activated reflex with vagal closure of the epiglottis and vocal cord. Adductor block of the airway is the most important function of the vocal cord. This reflex is activated by pharyngeal flooding. The motor limb of this reflex pathway is in the vagus nerve. Vomiting and aspiration have been observed in drowning, thereby complicating the physiologic phenomena.

In dysfunction of the reflexes protective of the airway the following complications are apt to prove fatal: vomiting, pharyngeal hemorrhage, and salivary pooling. Rapid flooding with resultant obstruction of the airway may preclude respiration. In less severe cases incomplete respiratory obstruction will occur. The latter is the case in partial bilateral medullary lesions.

The mixed pathways of the glossopharyngeal subserve the following specific structures and functions. Pain and temperature are mediated by sensory endings arising in the following structures: posterior third of tongue, pharynx, anterior surface of epiglottis, soft palate, uvula, tonsil, Eustachian tube, middle ear, medial surface of tympanum, and mastoid air cells.

Fibers mediating the above sensory modalities pass through the superior ganglion, the sensory rootlets of the 9th cranial nerve, and then enter the descending trigeminal tract and nucleus within the cord. After crossing to the opposite side of the spinal cord these fibers ascend to the thalamus.

Visceral afferent fibers arising in sensory endings in the same areas as the pain fibers pass to the inferior ganglion, the sensory root of the glossopharyngeal nerve, and the solitary fasciculus and nucleus. From this nuclear complex visceral afferent fibers proceed to visceral reflex centers affecting respiratory, cardiac, vasomotor, secretory, and visceromotor functions.

Gustatory fibers from the posterior third of the tongue proceed to the solitary nucleus where they are joined by taste fibers of the trigeminal and vagus nerves. All taste fibers then ascend to either the visceral reflex centers or the hippocampal center for taste. A galvanic current of ¼ milliampere applied to the posterior third of the tongue tests acid perception.

The carotid sinus nerve of Herring arises in pressor-receptors located in the adventitia of the internal carotid artery distal to the bifurcation and in

chemo-receptors in the carotid body. Fibers arising in the carotid body travel solely in the glossopharyngeal while a few fibers from the carotid sinus (dilated proximal part of the internal carotid artery) may enter the vagus nerve. Most of the fibers arising in the carotid sinus enter the glossopharyngeal nerve.

After entering the medulla, the carotid sinus nerve fibers of the 9th nerve establish connections with various reflex centers, bombardment of which from the carotid sinus or body may result in one or more of the following*: bradycardia, cardiac asystole, vasodilatation, hypotension, dizziness, vertigo, syncope, or convulsions. The efferent limb of the sinus reflex arc to the heart subserving the above cardiovascular effects is in the vagus nerve. Reduced cerebrovascular blood flow results in the above cerebral signs.

The tympanic nerve of Jacobson supplies preganglionic parasympathetic fibers to the parotid glands for salivary secretion mediated by the inferior salivatory nucleus. These fibers pass through the tympanic branch, the tympanic plexus, the small superficial petrosal nerve, and synapse in the otic ganglia. Retroganglionic fibers pass through the auriculo-temporal branch of the trigeminal nerve enroute to the parotid and salivary glands. Jacobson's nerve also transmits sensory and ventilatory fibers from the mucous membranes of the middle ear and Eustachian tube.

Special visceral efferent fibers arising in the glossopharyngeal complex of the nucleus ambiguus are motor to the constrictors of the pharynx and stylopharyngeus muscles. These elevate the pharynx and larynx, and increase the transverse diameter of the pharynx in preparation for swallowing.

Clinical syndromes of this nerve which have contributed to our knowledge and are of interest occur in trauma, herpes zoster, infections, hyperactive carotid sinus reflex, carotid body tumors, glomus jugulare tumors, and malignancies. Much of our information of glossopharyngeal function has been derived from studies of glossopharyngeal neuralgia.

Although glossopharyngeal neuralgia usually follows a pattern, there are certain variations. Temporal and anatomic variability of glossopharyngeal neuralgia is characterized by the following. The age of onset in essential cases is commonly after the 5th decade, although symptomatic cases may begin at a younger age. In the latter an organic causative lesion frequently can be demonstrated.

In essential cases the onset may be insidious or abrupt. Once established the disease usually persists. However, it may disappear for years. Remissions and intermissions are characteristic of milder cases. The single paroxysm of pain usually lasts a minute or two. The pain, as in other ganglionic disturbances may recur periodically every few minutes until an intermission occurs.

Essential glossopharyngeal neuralgia is a unilateral affliction. The trigger area may be in the lateral wall of the pharynx near the Eustachian tube or root of the tongue, in the external ear area posterior to the ramus of the mandible, or in both. The trigger and pain, after many years residence in one area, without known cause may shift to the other area. The trigger area may be "fired" by various stimuli. Commonly effective ones are swallowing and talking. Masticating, yawning, and coughing also stimulate the trigger mechanism. In Laskiewicz's[19] cases pronunciation of the throat consonants,

*The effects should not be confused with those resulting from carotid occlusive compression in the patient with atherosclerosis.

g, k, and l, produced paroxysms of neuralgia. Lateral movements of the mandible and exposure to cold are also effective. Stroking of the torus tubarius with an applicator is frequently effective in precipitating a paroxysm. Pressure behind the ramus of the mandible or around the ear may fire the ear trigger.

The severity of the neuralgic pain is excruciating. There may be burning pain in the tongue, pharynx, and palate. All trigger area stimuli are avoided by the patient. One patient refused food and fluid until section had been performed. As a result of pain even saliva could not be swallowed. In such cases emaciation is usually present.

As a paroxysm develops, the patient may grasp his head firmly with both hands and may stamp his feet, tom-tom dance-like. At the climax of pain there is homolateral tearing and salivation. Overflow unto the cheek and chin may be observed. This results from neuronal bombardment of the lacrimal and parotid glands.

After having withstood a number of paroxysms of neuralgia without treatment the patient may threaten suicide. In 2 of my patients this was the introductory remark.

The patient frequently complains of tinnitus and partial deafness between attacks. He notes that there is loss of hearing for whisper and low tones. This hearing deficit may be caused by tubal insufficiency. Tic-like movements are occasionally observed in the face between and during attacks.

In the differential diagnosis of tic douloureux of the 5th and 9th cranial nerves a pathognomonic sign of the latter is temporary relief from the pain after cocainization of the lateral pharyngeal wall. This not only temporarily relieves the spontaneous attacks, but also deactivates the pharyngeal trigger area for the duration of the anesthesia. Cocainization may fail to deactivate the pharyngeal trigger in rare cases. As in essential trigeminal neuralgia, the essential type of glossopharyngeal neuralgia has been characterized by a lack of any consistently recognizable pathogenetic lesion.

There have been occasional examples of causative abnormalities in symptomatic neuralgia, mostly malignancies. Examples of lesions resulting in symptomatic glossopharyngeal neuralgia have been reported as follows. The first case of the malady was reported by Weisenburg[44] in 1910 in a patient with a cerebello-pontine angle neoplasm. Interestingly, this patient had trigeminal neuralgia as well as the glossopharyngeal type. The latter was not recognized until the patient was relieved of the trigeminal neuralgia by surgical rhizotomy performed by Frazier. A second example is a case of glossopharyngeal neuralgia reported in 1954 by Permin[26]. This patient had a stenosing cancer of the upper esophagus. Brihaye, Perier, Smulders, and Franken[4] reported a case of glossopharyngeal neuralgia in which exitus occurred shortly after development of the tic. Examination post mortem revealed an atheromatous vertebral artery compressing the 9th cranial nerve. Inflammatory lesions resulting in 9th cranial nerve neuralgia have been described.

In 1920 Sicard and Robineau[35] reported 3 cases of "algie vélopharyngée essentielle" (tic douloureux of the glossopharyngeal nerve). They assumed that this affliction was a disease of the 9th and 10th cranial nerves and the cervical sympathetics. Accordingly, they sectioned all of these structures. This was the first attack on the glossopharyngeal nerve in the treatment of its neuralgia. In 1921 Harris[16] described 3 cases of neuralgia of the 9th cranial nerve and christened

the syndrome, glossopharyngeal neuralgia. In 1923 Doyle[11] reported 4 cases of glossopharyngeal neuralgia. In 2 of these cases a preoperative diagnosis of trigeminal neuralgia had been assumed and the patients subjected to section or injection of the sensory root of the 5th cranial nerve without relief. One of Doyle's patients was observed to have an attack of hacking cough during each neuralgic paroxysm.

The suggestion of Spiller that supraganglionic section of the sensory root of the 5th cranial nerve would abolish pain in trigeminal neuralgia pointed the way to successful treatment of glossopharyngeal neuralgia. Frazier successfully relieved trigeminal neuralgia by supraganglionic section prior to 1910 in which year Weisenburg first described glossopharyngeal neuralgia. In 1924 Adson[1] reported that cervical avulsion of the 9th cranial nerve was an unsatisfactory method of treatment of glossopharyngeal neuralgia. He suggested that intracranial supraganglionic section would be a more effective procedure.

In 1927 Dandy[9] reported, in 2 cases, the first successful relief of glossopharyngeal neuralgia by intracranial supraganglionic section. Dandy listed the advantages of this operation as follows. Supraganglionic section precludes recurrence because regeneration is impossible. The vagus and other nerves or vessels are not injured as in cervical approaches where malignancy may obstruct any surgical approach. In the Dandy operation the trigeminal root may be sectioned at the same sitting. This is particularly desirable if the case is one of malignant disease. This has also been noted by Peet[25]. Dandy demonstrated the following homolateral defects following intracranial section of a glossopharyngeal nerve: complete loss of taste in the posterior third of the tongue, anesthesia of nasopharynx, posterior pharyngeal wall, palatine tonsillar area, and inferior surface of the soft palate, and few subjective complaints.

Stookey[37] reported a case of glossopharyngeal neuralgia relieved by intracranial section of the rootlets of this nerve. He stated, as had Dandy, that the motor and sensory deficit of intracranial section of the rootlets of this nerve are practically unnoted by the patient. Stookey believed that the *rideau* sign is indicative of vagus nerve paralysis and not secondary to a glossopharyngeal nerve lesion as stated by Vernet.

Information relating to the glossopharyngeus has been gained from observation of lesions of this and related nerves. During World War I, largely as a result of numerous traumatic injuries to the neck, the glossopharyngeal nerve was carefully studied by a number of excellent investigators. In wounds of the neck, multiple injuries of the cranial nerves and vessels are common. Vernet[40,41,42] described associated unilateral lesions of the 9th, 10th, and 11th cranial nerves. This combined injury he termed the syndrome of the posterior lacerated foramen or of the jugular foramen. Collet[7] and Sicard[34] described involvement of the four bulbar nerves in lesions of the condyloposterior lacerated foramen. In addition to the findings in Vernet's syndrome, Collet and Sicard added atrophy of the tongue. Villaret[43] described the syndrome of the retroparotid space. In this the bulbar nerve paralyses are combined with Horner's syndrome. The latter is a result of involvement of the cervical sympathetics.

After World War I, Pollock[27] in a review of extracranial injuries involving the bulbar nerves, stated that prior to that time associated lesions of the extracranial portions of those nerves

had rarely been observed. These injuries occurred frequently during the first World War.

Elkin and Woodhall[12] reviewed the vascular and neural injuries of the neck which had occurred in World War II. This study concerned itself with glossopharyngeal and associated bulbar nerve injuries. They stated that the number of various combinations of bulbar nerve injuries below the base of the skull is legion. The fact of their associated injury is of little clinical import in traumatic disease. They advised a conservative attitude in the treatment of combined vascular and neural injuries of the neck. Studies of such injuries in these two war eras provided a greater understanding of glossopharyngeal nerve function.

Glomus jugulare tumors arising presumably in jugular vascular elements, postero-inferiorly to the middle ear, frequently compress the bulbar nerves in an area between the retro-parotid space laterally and the jugular foramen medially. These tumors also cause deafness and facial paralysis by expansion within the middle ear. They then infiltrate or perforate the tympanum. Secondary carotid sinus attacks have not been reported.

McSwain and Spencer[22] have reported 2 cases of carotid body tumors associated with an hyperactive carotid sinus syndrome. Extirpation of the sinus and tumor relieved the patient's symptoms in one case. Hyperactive carotid sinus syndrome occurs in about 5% of carotid body tumor cases.

In 1933 Weiss and Baker[45] reported a patient in which bradycardia, cardiac standstill, convulsive seizures, and fall in blood pressure followed stimulation of an hyperactive carotid sinus reflex. Section of the carotid sinus nerve by sinus stripping relieved this patient of his sinus symptoms. In a patient with 9th nerve neuralgia secondary to cancer of the tonsil they noted in sectioning the glossopharyngeal nerve that the blood pressure immediately increased from 95/65 mm. of Hg to 175/100 mm. Hg for a period of 40 minutes. Kezdi postulated glossopharyngeal demyelination as the cause of hypertension in a patient with porphyria[17a].

Wycis[46] sectioned the glossopharyngeus bilaterally in a patient with an epipharyngeal neoplasm for relief of pharyngeal pain radiating into both ears. As a result of this bilateral section the pain was completely relieved, the gag reflex was lost and the pharynx was analgesic to pin point and deep pressure. Dysphagia did not occur. Hypertension occurred immediately after section and persisted. Hypertension following glossopharyngeal denervation had been observed by Bucy[5]. Hypertension was not observed by Capps and deTakats[6] following bilateral carotid sinus denervation.

Reichert and Poth[30] demonstrated a 3-month depression in secretory activity in the parotid, sublingual, and submaxillary glands after unilateral glossopharyngeal nerve section. In 1934, Reichert[29] produced an incidental 6-day bradycardia of 40 after separating the 9th from the 10th cranial nerve intracranially. He also stated that Jacobson's tympanic branch neuralgia was relieved by intracranial unilateral section of the glossopharyngeal nerve. In 1942, Riley, German, Wortis, Herbert, Zahn, and Eichna[32] first reported 2 cases of unilateral glossopharyngeal neuralgia whose paroxysms of pain were associated with vasodilation, hypotension, syncope, cardiac arrest, and generalized convulsions. They believed that sensory endings in the carotid bifurcation mediated such reactions through central connections with cardiovascular centers, and that the efferent limb of the reflex arc to the heart was the vagus nerve. Herbert, Zahn,

Ryan, and Eichlin[17] reported 73 cases of glossopharyngeal neuralgia treated in thirty instances by supraganglionic intracranial unilateral section without a fatality. They also reported the successful relief by the same operation of hyperactive carotid sinus reflex associated with asystole and convulsion.

Spurling and Grantham[36] observed that in glossopharyngeal neuralgia the trigger area may be in one ear for several years and then shift to the homolateral throat. In cases with equally active trigger areas in both throat and ear, cocainization of the throat trigger did not inactivate the ear trigger. This suggests separately innervated trigger areas. It was their opinion that the ear trigger was innervated by the vagus nerve. For this reason they recommended that in cases with two trigger areas not only should the glossopharyngeal nerve be sectioned supraganglionically, but also the upper two strands of the vagus nerve should be sectioned. Dandy had recommended that same procedure when ear pain was severe.

Ray and Stewart[28] reported a case of glossopharyngeal neuralgia associated with hyperactive carotid sinus reflex symptoms of bradycardia, hypotension, syncope, and asystole. In this patient pressure over the carotid sinus precipitated both the neuralgia and the sinus attacks. Cocainization of the pharynx was *not* effective in relieving either the neuralgia or sinus attacks. This patient was surgically relieved by intracranial section of the glossopharyngeal nerve.

Roulhac and Levy[33] reported a patient in whom left glossopharyngeal neuralgia was complicated by convulsions of sinus nerve origin. Digital pressure over the left carotid sinus was without effect. However, stimulation of the left tonsillar fossa area precipitated the two component syndromes, the neuralgia as well as convulsion and asystole. Both components were relieved temporarily by cocainization of the left tonsillar area, and permanently by intracranial section of the glossopharyngeal nerve and upper two vagus rootlets.

Richburg and Kern[31] demonstrated that in a patient with combined attacks of glossopharyngeal neuralgia and hyperactive carotid sinus syndrome, atropine prevented the bradycardia, syncope, and convulsion. Atropine did not prevent the neuralgia paroxysm, however. These effects of atropine had previously been surmised by Ray and Stewart. Richburg and Kern believed that glossopharyngeal trigger stimulation resulting in central bombardment effected a vagal bradycardia. They postulated that hypotension and seizures resulted from similar central effects. These authors suggested that a rational medical regimen for patients with these syndromes be followed until surgery can be performed. This regimen consisted of cocainization of the trigger area and atropinization. Procaine injections can be employed also in an ear trigger neuralgia.

Thomson[38] resected the glossopharyngeal rootlets in a patient with glossopharyngeal neuralgia attacks accompanied by convulsion. He believed that excessive afferent glossopharyngeal trunk stimuli caused the seizures as digital stimulation of the carotid sinus was without effect.

Baker[3] and Love[21] affirmed the position of Dandy, Spurling, and others, Love stating that supraganglionic intracranial section of the glossopharyngeal nerve and upper rootlets of the vagus nerve will probably remain the operative treatment of choice in essential glossopharyngeal neuralgia. Uhlein, Love, and Corbin[39] reported equal sex incidence in their cases of glossopharyngeal neuralgia. Observation following supraganglionic section sug-

gested to these authors that the glossopharyngeal nerve subserved pain sense in the pharynx and the vagus subserved other sensory modalities.

In laryngeal vertigo (tussive syncope), first described by Gasquet and Charcot in 1822, etiologic factors remain obscure. Laskiewicz[20] refers to this as ictus laryngis. He describes this as a protective laryngeal reflex occurring in two forms. The mild form is limited to itching and soreness in the throat, paroxysmal cough and frequent strong inspirations. The serious form consists of the above symptoms in combination with feelings of weakness and short periods of unconsciousness. Attacks were precipitated by stimulating the laryngeal mucosa, by compressing the larynx externally, or by touching the posterior wall of the external auditory meatus.

Laskiewicz reported one patient who in recovery from herpes zoster of the glossopharyngeus developed attacks of glossopharyngeal neuralgia accompanied by short periods of weakness and unconsciousness. As the attacks were precipitated by turning the head, he believed that nerve fibers to the carotid body were placed on traction. As a result of this traction a carotid body reflex through the carotid sinus fibers produced a clinical state similar to ictus laryngis. He referred to this as ictus pharyngis. In this syndrome glossopharyngeal neuritis was present.

Prolonged rapid coughing and the Valsalva maneuver have also been observed to precipitate ictus laryngis. Increased intrathoracic pressure is common to these two precipitants.

In 1957 Asherson[2] described 5 cases of glossopharyngeal neuralgia with severe ear pain. In each case an elongated styloid process was palpable in the lateral pharyngeal wall. This abnormality could be visualized radiographically. Removal of the styloid process in 4 of these cases relieved the glossopharyngeal neuralgia.

Another syndrome involving the glossopharyngeus is that of herpes zoster. Hunt postulated that geniculate ganglionitis was responsible for so-called "otitic herpes," even though the face was paralyzed and the pharynx vesiculated.

Neve[23] reported the case of a patient who after "cold exposure" developed fever and vomiting. On the left the following signs were present: pain behind the ear and in the posterior neck, facial palsy, herpetic vesiculation of the soft palate and tongue, and nerve type deafness. Interestingly, Neve referred to this entity as a posterior poliomyelitis of the ganglia of the left 7th, 8th, 9th, and 10th cranial nerves and the 2nd and 3rd cervical spinal nerves.

O'Shea[24] described a patient who "after exposure to a draft" developed unilateral herpetic vesiculation on the right of the face, conjunctiva, neck, pinna, auditory meatus, tympanum, tongue, and pharynx. The patient also complained of severe pain and deafness in the right ear. O'Shea referred to this symptom complex as otitic herpes zoster. It seems probable that unilateral herpetic ganglionitis and neuritis were responsible.

Engstrom and Wohlfart[13] reviewed the literature of herpes zoster of the glossopharyngeus and reported 5 cases in which there was unilateral involvement of both the glossopharyngeus and vagus. In these patients there was hemiplegia of the pharynx and larynx. Vesiculation of the anterior lateral portion of the tongue, tonsillar region, palate, pharynx, auricle and external auditory canal was noted. Facial palsy, deafness, vertigo, and signs of infection were present. Three of their patients had pleocytosis of the cerebrospinal fluid.

Font[14] reported 2 cases of unilateral "jugular foramen syndrome" secondary to virus infection. In these cases, pharyngo-laryngeal vesiculation was associated with paralysis of the palate, pharynx, and larynx. In addition, there was loss of taste on the posterior third of the tongue, and paresis of the sternomastoid and trapezius muscles. This is the clinical picture of the homolateral associated involvement of the 9th, 10th, and 11th cranial nerve innervations secondary to infectious ganglionitis of the brain stem.

Denny-Brown, Adams, and Fitzgerald[10] reported pathologic studies of herpes zoster. They remarked that Hunt failed to study the geniculate ganglion pathologically and that their own studies indicated that Hunt's concept of geniculate herpes was invalid. Denny-Brown, Adams and Fitzgerald demonstrated that herpes zoster is a unilateral neuritis, radiculitis, ganglionitis, and segmental posterior poliomyelitis.

Grinker and Bucy[15] remark that the chain of parapharyngeal lymph glands extending to the subparotid gland, passes between the 12th cranial nerve medially and the 10th and 11th cranial nerves laterally. This chain lies in close proximity to the glossopharyngeal nerve and the cervical sympathetic chain. They point out that parapharyngeal adenopathies, therefore, result in multiple bulbar nerve involvement and Horner's syndrome. The syndromes of Vernet, Collet and Sicard, or of Villaret may occur in neoplasm of the cervical nodes. These deep cervical lymph nodes drain the hilar lymphatics of the lung. It is a common observation that the deep cervical nodes near the base of the skull are involved in metastatic malignancy either primary in or filtering through the thorax.

The gag reflex consists of constriction of the pharynx in response to a sensory stimulus applied to the posterior pharyngeal wall. Most afferent fibers in this reflex are in the glossopharyngeal nerve. The efferent fibers are believed to be entirely vagal. The reflex is inactivated in analgesia of the pharynx. Hysteria may mask the gag reflex bilaterally. In nuclear or infranuclear lesions of the glossopharyngeal or vagus nerves the reflex is absent on the side involved. The glossopharyngeal nerve also participates in the following reflexes: palatal, swallowing, salivary, sucking, and vomiting. Vernet's *rideau* phenomenon consists of draw-drape movement, toward the normal side, of the pharyngeal wall in saying, "ah." This sign is often present homolaterally in a lesion of the glossopharyngeal-vagus reflex arc. In such lesions the drape effect may be absent and the pharynx observed only to shift toward the normal side.

Pharyngeal paralysis, unilateral or bilateral, may occur following diphtheria, sometimes as a part of a polyneuritis or as a mononeuritis. Spasm of the pharynx may occur in tetanus, rabies, convulsions, and in posterior fossa neoplasms. Painful swallowing may occur in scleroderma, the asialorrhea of glossopharyngeal nerve paralysis or in the Plummer-Vinson syndrome. Cancer of the tongue, pharynx, and esophagus not infrequently causes continued painful swallowing.

Conclusions and Summary. The glossopharyngeus contains afferent and efferent fibers. The former arise in the superior and inferior ganglion located extracranially in the jugular foramen. The afferent tracts of the glossopharyngeus include the sensory limb of a reflex arc of which the vagus is the motor efferent. This arc synchronizes the organs of speech, swallowing, and respiration. A second sensory tract, the carotid sinus nerve of Herring, arises in chemo- and pressor-receptors in the

carotid body and carotid sinus, respectively. The sinus nerve is also an afferent limb of a reflex arc of which the vagus is a motor efferent. This reflex arc and its medullary ramifications affect vasodilator, vasoconstrictor, cardioinhibitor, and respiratory cell centers. A third sensory tract subserves pressure pain for ventilation of the middle ear and Eustachian tube. A fourth special sense tract carries taste impulses from the posterior third of the tongue.

The efferent motor pathways of the glossopharyngeus elevate the pharynx in swallowing. The efferent secretory fibers innervate the parotid gland. Hemianalgesia and unilateral loss of the gag reflex occur in unilateral nuclear or infra-nuclear glossopharyngeal lesions. Bilateral section of the glossopharyngeus results in analgesia to pin point and deep pressure in the pharynx. Painful swallowing occurs in glossopharyngeal neuralgia, cancer or infection in or adjacent to the pharynx, asialorrhea, scleroderma, and Plummer-Vinson syndrome. Spasm of the pharynx, secondary to irritation of the vagus may occur in rabies, tetany, tetanus, and posterior fossa lesions.

Glossopharyngeal neuralgia, an irritative and unilateral lesion consists of pain in the lateral pharyngeal wall or between the external ear and the ramus of the mandible. The trigger zones are frequently found either in the lateral pharyngeal wall or around the external ear. Essential glossopharyngeal neuralgia may be associated with the carotid sinus syndrome of asystole, hypotension, or cerebral ischemic convulsion. In this combined syndrome stimulation of the trigger zone or zones or the carotid sinus may produce simultaneous neuralgic pain and asystole, hypotension, or convulsion. Medical and preoperative treatment consists of local anesthesia and atropinization. Surgical rhizotomy of the glossopharyngeal and upper two vagus rootlets relieves the pain and sinus symptoms.

Symptomatic glossopharyngeal neuralgia may occur in malignancy of the pharynx, in posterior fossa tumors, or aneurysms compressing the intracranial rootlets. Herpes zoster is a virus infection primarily of a single sensory ganglion. If spread of infection occurs in glossopharyngeal herpes zoster only homolateral involvement results. In extension of the infection the facial, auditory, vagus, and spinal accessory nerves may be involved.

The glossopharyngeus is involved in many syndromes and disease states. These ramify into many fields of general medicine and the specialties. Interest in the glossopharyngeal nerve accordingly is broad.

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MEDICINE

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CARDIOVASCULAR DISEASES IN THE WHITE AND NEGRO RACES*

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I. Introduction. A. GENERAL. THIS is a review of selected aspects of the incidence of cardiovascular diseases in the white and Negro races. A study of well over 1,000 reports dealing with racial factors in cardiovascular disease revealed the difficulties concerned with investigations of racial relationships in cardiovascular disease. Numerous factors must be known, controlled and properly evaluated for proper interpretation. Unfortunately, many of the studies referred to in this review fail to meet these requirements but may indicate possible trends. Reliable interpretations of any study in racial relationships in cardiovascular disease require consideration of at least the following factors:

1. Differences in population distribution for the community from which the subjects in the study are derived.
2. Racial admission rates to the particular institution.
3. Racial mortality rates.
4. Racial necropsy rates.
5. Socioeconomic influences upon admission to either private or public institutions.
6. Qualification of the clinician, adequacy of diagnostic facilities, and nature and accuracy of methods employed to establish diagnosis.
7. Role of the investigator in the clinical and other studies of the patient. Were hospital records simply reviewed?
8. Control of age factors; patients die before arteriosclerosis and other diseases can develop.
9. Influence of sex; racial differences may be amplified, nullified, or reversed by sex.

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10. The influence of the associated diseases upon the particular conditions under study.
11. The influence of factors such as exposure to climate and weather, malnutrition, and accidents; this is especially important in studies in the tropics.
12. The influence of age factors in different countries where life expectancy is low; for example, India and Africa. Those who live longer might be healthier and hardier people less prone to develop hypertension, arteriosclerosis, and other diseases.
13. Training, level of interests and prejudices and objectivity of those who actually conduct the study.
14. Type of material from which the data were selected. The difficulties concerned with death certificates is well known[69,134]. For example, it was shown recently that the alleged low incidence of coronary artery disease in France was not due to the dietary use of olive oil, as suggested, but to a different habit of certification by French doctors[127].
15. The nature of the diagnostic criteria employed, both clinical and pathological.
16. Extent and severity of the particular disease under study.
17. Is the sample studied truly representative? Do hospital and institutional studies reflect community trends[183]?

The variables differ with studies and some may not be controllable. Conclusions are impossible and the study is useless or misleading with inadequate conditions of study. For example, many published studies contain definite conclusions of racial incidence of disease without consideration of racial admission rates for the particular institution. In most of the reports reviewed, the reader is obliged to assume that the most basic variables were controlled by the investigators. If this is true the data discussed in this report are sufficient to show only *trends* of the racial incidence of cardiovascular disease. In many instances such assumptions are probably in error.

Be not misled by the color of the skin. Skin color has caused separation and selection among peoples with resultant propagation of differing genetic characteristics. These genetic characteristics then form the background upon which differences in racial incidence and manifestation of disease become possible. This is true of cardiovascular diseases.

This discussion is concerned primarily with the American Negro and white races. Data concerning whites from outside the United States and the African Negro were included to amplify the discussion.

B. HISTORICAL DATA. Slavery in America did not actually begin until 1619 following a chance landing in Jamestown of a Dutch vessel carrying a cargo of African bondsmen. For over 100 years previous to this, Negroes had been present in the New World. They had been used as slaves in the West Indies since 1502 and had acted as companions for the Spanish explorers shortly after this time; many of them landed in what is now Florida, Virginia and South Carolina. During the years from 1619 to the start of the American Revolution in 1776, more than 300,000 African slaves were imported into the 13 British colonies[132,146].

Because of the diversity of the various tribes inhabiting the West African Coast which supplied the greater portion of the slaves, a great variety of Negro types were first introduced into the British colonies in America. The types were so grossly different that each was readily recognizable by their

mental characteristics and physical capabilities. In the course of time, however, the various types were gradually fused and it may be said that the African contribution to the American Negro is probably a composite of all of the genetic characteristics of the various West African tribes.

C. THE AMALGAM OF THE AMERICAN NEGRO. Since their importation only 300 years ago the American Negroes have become a new, distinct group of people, the product of three principle racial stocks of the world, the African Negro, the Caucasian, and the Mongoloid (American Indian)[87]. Since the Negro's first arrival in North America there has been a great deal of miscegenation. The wide diversity in the African tribes providing the Negro contribution has already been noted. The Caucasians from America came from different peoples of Northern, Central, Southern, and Western Europe. The Indian contributions were from a population of diverse tribes mainly from southeastern North America and the Caribbean Islands. The extent of which each racial stock contributed to the final product of the American Negro has been a source of considerable debate and remains unsettled[65,66,87,88,89,96,132,171,180,212]. Nevertheless, there is general agreement that the American Negro, regardless of background, constitutes a distinct physical type, and the term "American Negro" has accepted biological connotations.

II. Anthropological and Basic Anatomical, Physiological, Pharmacological and Pathological Aspects of the Cardiovascular System. A. ANATOMY AND GENERAL ANTHROPOLOGY. Several studies have appeared in the literature describing racial variations in the anatomy of the cardiovascular system. Slight to moderate differences in the arterial system between the white and Negro races (chiefly of questionable statistical significance) have been described. Statistically significant differences were mainly in the aortic arch and its branches[41,140,187,243,244]. Although these anatomic differences are minor from the clinical point of view, they are morphologically important.

Studies on the venous system have shown slight to moderate racial differences of questionable statistical significance for several groups of veins. One detailed study of the azygos system of veins[203] showed statistically significant racial differences.

Blache and Handler[19] reported that American Negroes more frequently have coronary ostia situated above the line of closure of the aortic valve cusps than whites. Brink[24,25] found the Bantu to have an extra large branch of the left coronary artery which originated near the orifice of this vessel. This large branch coursed posteriorly over the myocardium to the posterior obtuse border of the heart. The author considered this to be partly responsible for the low incidence of myocardial infarction in the Bantu. This observation has not been confirmed[196]. Dick[44] found the thoracic aorta in East African natives to have a circumference that was significantly smaller than that for Europeans of the same body size.

B. PHYSIOLOGY AND PHARMACOLOGY. Most investigations regarding physiological functions have been concerned with thermal regulation. It would appear that a part of these physiological characteristics of the Negro are inherent in the skin and associated with the adaptation to the tropical climates peculiar to Africa. The functions of skin pigment, dermal vessels, sweat glands and the Negro's superior adaptation to hot and humid environment have been studied[109,132,144,175,184].

Of interest have been recent studies by Meehan[147] concerning individual and racial variations in the vascular

response to a cold stimulus. He noted that Negro military personnel had a significantly higher percentage of cold injury, particularly of the extremities, than did the white personnel. Controlled experiments were designed to test the cold adaptation among three racial groups, namely, Caucasians, Negroes, and Alaskan natives. The subjects all had similar environmental exposure preceding the test. The experiment involved recording surface finger temperatures during a 30-minute ice water immersion period. The Alaskan native maintained the highest finger temperature during the immersion period, and the Negro the lowest. Caucasians differed little from the Alaskans. The findings indicated a possible physiologic adaptation to cold on a racial, as opposed to an individual basis, and this offered a physiological explanation for the higher percentage of cold injuries seen in the Negro military personnel.

Schwab[198] observed the response to the cold pressor test in 172 whites and 152 Negroes between the ages of 15 and 35 years. The arterial blood pressure rose more in the Negro than in the white suggesting a quantitative racial difference in the reaction to the standard vasomotor stimulus. This may indicate a more sensitive vasomotor mechanism in the Negro than in the white.

Little attention has been devoted to racial variations in response to cardiovascular drugs. Paskind[169] studied the racial differences in response to atropine. He found the ultimate acceleration of the heart rate from parenteral administration of this drug to be the same for both races but the initial depression was greater in white people. He considered the Negro less susceptible to the central action of atropine than whites.

C. PATHOLOGY. Blache and Handler[19] have shown quantitative and qualitative racial differences in the pathogenesis of coronary atherosclerosis. They found the rate of development of coronary atherosclerosis in the Negro to lag behind that of the white by approximately 10 years. In addition, there were basic differences in the coronary artery elastic tissue elements. Holman *et al.*[94] demonstrated significantly more deposition of lipid in the aorta in Negroes at the time of puberty than in whites, but the Negroes had less tendency to convert the fatty streaks to fibrous plaques. Precise quantitation of such phenomena is difficult, however.

In further studies, Handler, Blache and Blumenthal[78] found, in contrast to changes noted in the coronary arteries, that the renal arteries appeared to age more rapidly in the Negro than in the white group. These changes with age consisted mostly of straightening, increasing in density, thickening of the internal elastic lamina, and progressive calcification of the external lamella and elastic elements extending into the media from both lamella. These changes appeared to be related to the higher incidence of hypertension in the Negro, probably more the result of hypertension than a cause of it. Similar racial differences were noted with respect to changes in the splenic arteries with age, but no definite conclusions were reached since the number of cases studied in this group was small.

III. Relative Incidence of the Various Etiological Types of Heart Disease. A. PREANTIBIOTIC ERA. Although the relative incidence of various etiologic types of heart disease in whites and Negroes is now different from that of 25 years ago prior to the introduction of antibiotic agents, the older data are reviewed for comparative and historical significance. The term "preantibiotic" is employed to include con-

TABLE 1.—RACIAL INCIDENCE OF HEART DISEASE IN PREANTIBIOTIC ERA

The investigators, year, and type of study are shown. The number of patients are indicated in parentheses.

Type	*Schwab and Schulze—1931—Clinical* (488)		(1172)		(1660)	*Hedley 1935 Clinical and Necropsy* (258)		(192)		(450)	*Holoubek 1945 Necropsy* (380)		(665)		(1045)	*Stone and Vanzant—1927—Clinical and Necropsy* (501)		(414)		(915)	*Laws—1933—Clinical* (365)		(280)		(645)	*Peery and Langsam—1939—Necropsy* (68)		(450)		(518)	*Gager and Dunn—1933—Clinical* (600)		(600)		(1200)	*Totals* (2660)		(3773)		(6433)
	W	%	*N*	%	*Both*	*W*	%	*N*	%	*Both*	*W*	%	*N*	%	*Both*	*W*	%	*N*	%	*Both*	*W*	%	*N*	%	*Both*	*W*	%	*N*	%	*Both*	*W*	%	*N*	%	*Both*	*W*	%	*N*	%	*Both*
Hypertensive	42		63		57						34		44		40	45		50		48																			
Arteriosclerotic	36		14		20	65		56		61											65		72		68	34		60		58	51		59		56	43		56		52*
Syphilitic	7		15		13	5		21		12	34		13		21	24		6		16						32		7		11	26		13		20	30		11		18*
Rheumatic	7		2		3	17		8		13	13		10		11	10		4		7	16		4		11	7		4		1	7		5		6	11		5		7
Thyrotoxic	3		2		3	1		2		1	0		1		1	1		1		1	1		1		1						4		1		2	1		2		2†
Congenital	1		1		1	2		1		2	2		2		2	1		1		1	4		2		3	2		1		1						2		1		1†
Miscellaneous	2		1		1	6		5		5	9		5		7	3		2		3	7		3		5	21		14		15	7		6		6	6		5		5
Unknown	2		2		2	4		6		5	0		1		1	6		4		5	5		3		4											3		2		2†

*Excludes those two studies where division between the hypertensive and arteriosclerotic group was not made.

†Excludes that study where this classification was not made.

(Percentages Reduced to Nearest Whole Numbers)

sideration of all chemotherapeutic antimicrobial agents introduced since the advent of sulfonamides. Although changed, these data might assist in the understanding of the influence of infections on racial differences in incidence of cardiovascular diseases, morbidity and mortality.

Table 1 summarizes most frequently quoted data of racial incidence of cardiovascular disease in the preantibiotic era. Unfortunately, these figures are employed by many to define present situations. Hypertensive cardiovascular disease led in incidence for both races. Next, for both races, was arteriosclerosis which was more frequent in whites. Third was syphilitic heart disease which was much more frequent in the Negro. Rheumatic heart disease was next, being slightly more frequent in the white race.

Although there have been considerable variations in data from various authors, the conclusions have, in general, been the same. In 1931, in an extensive study (10,188 patients, 4,252 whites and 5,936 Negroes) Schwab and Schulze[197] found that organic heart disease was 1.7 times more frequent in the Negro than in the white. In this study, hypertensive heart disease and syphilitic heart disease were respectively two and one-half times and four times more frequent respectively in Negroes than in whites, while arteriosclerotic heart disease was one and one-half times more frequent in whites. It was their impression that rheumatic heart disease also was significantly more frequent in whites.

In a later study, Schwab and Schulze[199] referred to reports by several authors who showed that the mortality from heart disease in the preantibiotic era was 80% higher for Negroes. The morbidity was also greater in the Negro. The differences were not due to socioeconomic factors. The etiologic incidence of cardiac disease for the preantibiotic era was similar in many other studies[3,26,40,48,59,82,98,125,132,133,155,159,172,173,174,197,199,213,248].

In 1935, Hedley[82] in a study of 450 fatal cases of heart disease (258 white and 192 colored) found Negroes died on an average of nearly 8 years younger than whites. The maximal number of fatal cases among both sexes of the white race occurred in the 60 to 69-year age group; this occurred in the 40 to 49 age group for both sexes in the Negro race. A much higher mortality was noted in the Negro during the 30 to 39-year period than among whites because of syphilis of the heart and aorta and earlier and more severe arterial hypertension among Negroes. Rheumatic heart disease was more common in the white race (especially females). Hypertension was especially fatal in the Negroes, more so among females, whereas atherosclerosis and thrombosis were relatively uncommon. Syphilis was more frequent in the South and rheumatic fever more frequent in the North[125].

Lewis[132] reviewed the racial incidence of disease in 1942 in his book, *The Biology of the Negro.* He noted that since 1928, heart disease had killed more Negroes than any other disease. This had been true for whites since 1912. Tuberculosis had previously ranked first for both races.

B. CHANGING PATTERNS OF HEART DISEASE IN THE POSTANTIBIOTIC ERA. The data described so far serve to indicate the problem before the early 1940's. When the many factors are considered which influence the racial incidence of disease, it becomes apparent that precise definitions of racial incidence of cardiovascular diseases have little significance[155,182]. Reliable, accurate quantitative information on the racial incidence of cardiovascular disease with respect to the entire population is not

available; only trends are known. Comparison of a large number of different studies is extremely difficult and conclusions obtained are subject to considerable doubt.

Changes in disease patterns are largely the result of the tremendous influence of antibiotic agents, manifested predominantly in the treatment of syphilis, bacterial endocarditis, tuberculosis and other infectious diseases, the prophylaxis of rheumatic fever, and the prevention of bacterial complications in cardiovascular disease. The influence of antibiotics upon the changing pattern of diseases is still strongly active and its ultimate potential has not yet been fully realized. Recent developments in therapy of hypertension and nutritional disease, dietary manipulations in obesity and metabolic abnormalities, steroid therapy and numerous other therapeutic, diagnostic, and public health measures must influence the incidence of disease. However, the advent of antibiotics to modern medicine has been the single most important factor[32].

Among the limited recent studies, those of Hutcheson, Hejtmancik, and Herrmann[107] in 1953 serve to illustrate the changes which have occurred in the racial incidence of cardiovascular disease over the last two decades (Table 2). Table 2 should be compared with Table 1. Hypertensive disease still heads the etiologic list in the postantibiotic era for cardiovascular disease for both races and probably has increased slightly in incidence. It remains more frequent in the Negro. Arteriosclerosis is in second place and is still considered more frequent in white people. Similar findings have been reported for these diseases by Lilienfeld[134] in a more recent study.

TABLE 2.—RACIAL INCIDENCE OF HEART DISEASE IN POSTANTIBIOTIC ERA OBTAINED FROM A CLINICAL STUDY OF 1000 CASES BY HUTCHESON, HEJTMANCIK AND HERRMANN—1953[107]

(Percentages Reduced to Nearest Whole Numbers)

	W(637)	*N(363)*	*Both(1000)*
Hypertensive	46%*	67%†	54%‡
Arteriosclerotic	31%	12%	24%
Syphilitic	1%	5%	2%
Rheumatic	7%	6%	7%
Thyrotoxic	1%	1%	1%
Congenital	9%	4%	7%
Miscellaneous	5%	4%	4%
Unknown	1%	1%	1%

*Includes 109 patients with arteriosclerosis
†Includes 75 patients with arteriosclerosis
‡Includes 184 patients with arteriosclerosis

This is probably erroneous[30], however. The conclusions reached vary with definitions and criteria which guide the investigator. Everyone beyond the age of 35 years must have at least two or more atherosclerotic plaques at some site in his arterial system; therefore, all people at that age or perhaps younger have atherosclerosis, but everyone does not have arterial hypertension. Under strict criteria, arteriosclerosis must be one of the most frequent causes of cardiovascular disease in the world today. Unfortunately, reports in the literature[107] fail to show this.

A truly remarkable change is reflected in the marked decrease in the

incidence of syphilitic heart disease in both races due primarily to penicillin therapy. New cases of cardiovascular syphilis are even much less than implied by reported data and late effects of cardiovascular syphilis are rapidly becoming a curiosity in many nations. Rheumatic fever has decreased in the white race but remains relatively unchanged in the Negro. The reported slight decline in the incidence of rheumatic heart disease probably does not portray an accurate picture. Included in the recent series are large numbers of patients with chronic rheumatic valvular disease, many of which were established in the preantibiotic era. Many more patients with chronic valvular disease are now being referred to medical centers from which distorted concepts of incidence are reported. The apparent relative increase in frequency of congenital heart disease (especially in the white race) described in the literature is difficult to accept. This may be due to the extensive interest in and publicity given to congenital heart disease, but is most likely due to the source of the reports and the nature of the criteria established for the definition and diagnosis of diseases of the heart and blood vessels[30].

Of the 1,000 patients with organic heart disease studied by Hutcheson *et al.*[107], 63.7% were white and 36.3% were Negro. The ratio of white to Negro patients admitted to clinics and hospital wards at the John Sealy Hospital at that time, however, was approximately 2:1. Considering this factor, the incidence of heart disease in the Negro probably was not significantly higher than among whites. The corrected ratio of 1.1:1.0 is of considerable interest in that it is much less than the 1.8:1 reported by Stone and Vanzant[213] in 1927, and the 1.7:1 recorded by Schwab and Schulze[197] in 1931.

A fairly recent (1956) study by Lilienfeld[134] of the racial incidence of arteriosclerotic and hypertensive heart disease for 1949–51 in Baltimore confirm other investigations. Mortality rates from arteriosclerotic heart disease were highest in white males, and progressively lower in white females, Negro males, and Negro females. Mortality rates for hypertensive disease were highest in Negro females, and progressively lower in Negro males, white females, and white males.

Studies[11,36,51,62,241] from Africa published during the last two decades on the incidence of heart disease on that continent are difficult to evaluate and compare among themselves as well as with studies from the United States. Numerous factors account for these difficulties, among which are differences in groups, races and tribes studied, different selective and diagnostic criteria, different methods of presentation of data and other factors.

C.COMMENT. Even though this review provides some insight into the racial trends of cardiovascular disease, the data are still misleading. A difficult problem resides in the simple definition of heart disease. For example, is a heart to be considered diseased if abnormal T waves in the electrocardiogram are the only disturbances noted? Hutcheson *et al.*[107] reported an incidence in the Negro of 4% for congenital heart disease and 4% for miscellaneous heart disease. Using the more subtle criteria obtained from electrocardiography, vectorcardiography, roentgenography, and similar data for the diagnosis of heart disease, the incidence of heart disease in patients with malnutrition, anemia, and infections is greater than both these former two groups combined. Sickle cell disease itself would significantly bolster this percentage in the Negro. Recent studies of the incidence of cardiovascular changes in influenza[230] reveal the im-

portance of systemic infection in causing heart disease. Unfortunately, reliable data concerning these factors are not available. Most published data are concerned with the gross and usually the irreversible forms of cardiovascular disease.

IV. Specific Cardiovascular Diseases. Considerable quantities of statistical data are available in many reports concerned with the various specific cardiovascular disease states for the white and Negro races but absolute values are probably not too reliable, therefore numerical values will be used to illustrate trends. Absolute values remain to be learned.

A. HYPERTENSION. Of all the racial studies of cardiovascular diseases, hypertension and arteriosclerosis have received the most attention. During the last two decades well over 150 reports have appeared in the English literature concerned with hypertension in the Negro alone. Clark *et al.*[34] gathered over 16,000 references concerning hypertension alone. In 1957 Lennard and Glock[128], in an excellent review of the epidemiology of hypertension in the United States, reached reasonably acceptable conclusions. However, considerable differences exist among studies. The most important of these variations have been: (1) variations in the definition of "hypertension" and in criteria of diagnosis of such diseases as essential hypertension, hypertensive heart disease, hypertensive cardiovascular disease, arteriolar hypertension, hypertensive cardiovascular renal disease, hypertensive arteriosclerotic heart disease, and others; (2) considerable variations appear in the method of obtaining the blood pressure; and (3) samples vary, there being largely selective groups rather than groups representative of the entire population. However, as noted by Lennard and Glock[128], "despite these variations in definition, in procedure, and in sample selection, and despite other inadequacies of somewhat less importance, it is nevertheless significant that these studies all support a similar conclusion; namely, that Negroes in the United States are more often found to suffer from essential hypertension, hypertensive heart disease, hypertensive cardiovascular disease, or related disorders, than whites. In fact, insofar as is known, no study has yet been done on a group of subjects in the United States which would support an opposite conclusion."

Thus, despite all variations the conclusions are remarkably similar[1,2,3,4,8,40,50,56,59,79,82,98,119,125,129,132,133,142,154,155,172,173,197,199,205,,213,215,236,237,248]. In general, the ratio of the incidence of hypertension in the Negro to the white is two to one or greater. All investigators agree that the magnitude is greater in the Negro than in the white with respect to: (1) average blood pressure level in normal people, (2) incidence of hypertensive disease, (3) morbidity from hypertension, and, (4) mortality from hypertension.

Mortality from hypertension is much greater in Negroes than in whites for both males and females[128]. This was true for every state studied in the United States and for every age group from 20 to 84 years (Table 3). From the ages of 30 to 55 the mortality in the Negro was from 5 to 9 times higher than for the white[128]. Similar findings were reported from Central America, Panama, and the Caribbean in that the Negroes of these areas have a greater incidence of hypertension than do the Caucasians or Panamanians[10,77,116,117,145,193,202,216].

Reports on blood pressure from Africa are incomplete and the interpretations are conflicting. This appears to be due to the factors listed previously but especially due to the difficulty in

TABLE 3.—DEATH RATE FROM HYPERTENSION WITH AND WITHOUT MENTION OF HEART DISEASE BY AGE, SEX, AND RACE FOR THE UNITED STATES (1950)*†

Race and Sex	*AGE (Years)*										
	20–24	*25–29*	*30–34*	*35–39*	*40–44*	*45–49*	*50–54*	*55–59*	*60–64*	*65–69*	*70–74*	*75–84*
	Hypertension With Mention of Heart Disease (Death Rate per 100,000)											
WHITE												
Male	0.4	0.7	1.6	3.6	9.9	21.8	46.9	82.9	133.0	219.2	350.4	749.5
Female	0.3	0.7	1.6	3.8	10.5	21.6	42.4	69.0	124.9	207.5	371.8	748.9
NEGRO												
Male	2.3	5.0	15.3	35.5	74.5	125.5	252.9	366.2	491.4	545.9	778.4	1525.2
Female	2.4	5.9	23.5	48.7	98.1	164.2	274.8	398.0	540.3	498.1	789.2	949.5
	Hypertension Without Mention of Heart Disease (Death Rate per 100,000)											
WHITE												
Male	0.3	0.4	1.1	1.9	3.6	5.4	8.1	11.0	16.0	26.4	48.1	110.6
Female	0.2	0.5	1.0	1.4	2.9	3.3	5.4	6.7	12.3	21.1	40.5	106.0
NEGRO												
Male	1.2	3.5	9.2	15.0	20.9	24.7	34.1	32.2	55.7	62.5	84.0	141.7
Female	1.1	4.0	8.8	16.3	23.0	24.8	32.9	41.9	65.0	50.0	71.4	122.1

*Sources for the above data were (*a*) Vital Statistics of the United States, 1950, Vol. III, and (*b*) the 1950 Population Census (PC 14, No. 13–19, Selected Summaries).

†From Lennard and Glock[128]

obtaining a representative sample of subjects for study. The groups differ widely. Some reports show that native Africans have lower arterial blood pressure than Caucasians and that hypertension is rare in the Negro[47,112,123,206,227,240] whereas others report hypertension not to be rare in native Africans but that it may even be more frequent than in Caucasians[11,15,62,81,165,217,225].

The cause of the difference in incidence in arterial hypertensive disease between the white and Negro races in America is unknown. Lennard and Glock[128] group the hypotheses of causes into four groups which in general need no explanation: (1) the genetic hypothesis, (2) the physical exertion hypothesis, (3) the psychosomatic hypothesis, and (4) the associated disorder hypothesis which suggests associated diseases lead to or exaggerate hypertension. Although evidence has been presented to support each of the above hypotheses, they remain hypotheses.

B. ARTERIOSCLEROSIS. Many of the criticisms directed toward the published investigations concerning the role of racial factors in hypertension could well be repeated here. Of even greater significance is the fact that early arteriosclerosis is frequently a very difficult diagnosis to establish by clinical means. Considerable variations exist in quantitating arteriosclerosis at necropsy. A single small atherosclerotic plaque located in the left coronary artery may be much more significant than many large plaques distributed throughout the abdominal aorta. Again the definition and usage of terms have varied from report to report, such terms as arteriosclerosis, atherosclerosis, arteriosclerotic heart disease, coronary artery disease, and others, are used interchangeably. These simple problems alone indicate the difficulties concerned with comparing studies. Therefore, emphasis must be on trends and not absolute quantities. The methods used in the investigations are only semi-quantitative, but these quantitative limitations do not imply that the methods are not useful. Recently developed procedures of Gore and Tejada[70] and Holman *et al.*[94,95] may help somewhat to overcome the difficulties concerned with the quantitation of atherosclerosis, but even these methods are still relatively crude. The problems concerned with planning and executing a satisfactory epidemiological study of arteriosclerosis today are enormous.

1. Arteriosclerotic Heart Disease, Myocardial Infarction, and Angina Pectoris. It has been almost consistently found that arteriosclerosis differs from hypertension in that it is more frequent in the white than in the Negro[8,19,29,57,59,82,98,100,106,142,252]. The reported ratios range from approximately 4:3[252] to 4:1[29]. The report of Mihaly and Whiteman[151] differs. They suggested in 1958 that arteriosclerotic heart disease was essentially as frequent in Negroes as in whites. Their data seem inclusive, however, since their patients were from a highly selected group of Negroes from the Harlem Hospital which is populated mainly by Negro patients.

Blache and Handler[19] in 1950 reported necropsy studies from four general hospitals in St. Louis. The incidence of myocardial infarction in whites averaged 19.5% for two hospitals whereas that for two Negro hospitals averaged 1.7%. Comparison of the arteries of corresponding age groups of the two races revealed that the rate of development of coronary arteriosclerosis in the Negro was slower than in the white by approximately ten years, the lag being most prominent during the fourth, fifth, and sixth decades. Qualitative differences were also noted. Employing

elastic tissue staining and micro-incineration, the elastic elements in the arteries of Negroes manifested a greater tendency to swell but a lesser tendency to fragment and calcify than the corresponding elements of the coronary arteries in white people. Their observations were in accord with the concept that the formation of intimal atheromatosis or atheromatous plaques is conditioned by the severity of the elastic tissue changes and subsequent calcification. As a side note these authors observed a greater number of the coronary ostia of Negroes to be situated above the line of closure of the aorta valve cusp than in the white[36,78].

Weiss and Gray[236] studied 54 Negro patients with myocardial infarction admitted to the Louisville General Hospital from 1942 to 1953. Ninety per cent of the Negroes with myocardial infarction had hypertension; 82.2% of the males and 92.2% of the females. The incidence of hypertension in white females with myocardial infarction was two to three times greater than in white males. Holman *et al.*[94] reported pathological differences between whites and Negroes in New Orleans. The Negroes apparently had significantly more lipid deposited in the aorta about the time of puberty but have a lesser or delayed tendency to convert the fatty streaks to fibrous plaques. These studies need confirmation by more extensive biochemical methods.

Using the method of Gore and Tejada[70], Robertson[182] has compared Jamaicans (mostly Negroes) with Negroes from Guatemala and New Orleans reported by the former[217]. The three groups differed little in severity of aortic atherosclerosis until the third decade. Thereafter, the Jamaican and New Orleans groups showed a very similar sharp upward trend. This trend was not seen until the fifth or sixth decade in the Guatemalan group, and even then was much less steep.

Tejada and Gore[217] found in their two groups that the incidence of atherosclerosis in the aorta paralleled the incidence of ischemic heart disease, both of which are common in New Orleans but rare in Guatemala. It is extremely interesting, however, that Robertson[182] did not find this relationship to exist in Jamaica. The incidence there of atherosclerosis was almost identically as high for the various ages as in New Orleans, but the incidence of ischemic heart disease was relatively low, almost as low as in Guatemala. Such differences among reports are difficult to interpret. The incidence of myocardial infarction in the patients in New Orleans was 16.1%, in Guatemala 0.4% and 2.4% in Jamaica. Apparently, then, although the Jamaican Negro developed a degree of aortic atherosclerosis comparable to that of the Negroes in New Orleans, only occasionally did he succumb to ischemic heart disease. Tejada and Gore[217] unfortunately felt that the number of patients was not sufficient to justify separate evaluation of the white and Negro material from their New Orleans studies. Robertson[182] concluded that Negroes are as liable to develop severe aortic atherosclerosis as are whites but much less likely to develop ischemic heart disease. This idea is not new, however. Groom *et al.*[74,75] studied 267 necropsy specimens, 139 Negro adults from Charleston, South Carolina, and 138 from Haiti. These two groups were selected because of their common origins, for the most part West Africa. It was found that the Negroes from the United States showed about twice as much atherosclerosis of their coronary arteries as did the Haitians. The aortas, however, showed no such difference. The lack of correlation in certain racial groups between aortic atherosclerosis

and coronary occlusion has been reported in studies from Africa.

In summary, these and many other studies[56,113,125,132,133,136,153,172,173,181,197,199,207,213,234,235,237,248] support the same general conclusions: that arteriosclerotic heart disease (including myocardial infarction and angina pectoris) is more frequent in whites than in Negroes, but that the Negroes who die of this disease do so at an earlier age than the whites. The influence of other associated diseases upon the racial difference and the possibility of racial differences in the clinical manifestation of arteriosclerotic heart disease have not been settled. The data are vague and conflicting. Of extreme interest is the tendency for the white male to white female ratio for arteriosclerotic heart disease to be much greater than the colored male to colored female ratio[59,100,142]. This offers data for interesting speculation not only for racial differences but for sexual differences. More recent reports show a tendency for the white and colored differences to narrow. The reasons for this are unknown.

Numerous theories have been advanced to explain these apparent differences in arteriosclerosis between the whites and Negroes. The more frequently introduced factors include basic genetic differences, basic tissue differences, differences in cardiovascular anatomy and physiology, differences in diet, variations in socioeconomic factors including stress, differences in associated diseases, and hematologic differences (including viscosity and coagulability of blood). Since these factors are only hypothetical and have few supporting data, they will not be discussed.

The racial data from Africa concerning arteriosclerotic heart disease are not nearly so conflicting as are the data originating in Africa for hypertension. Schrire[194] recently (1958) studied the racial incidence of myocardial infarction in 12,512 electrocardiograms of adults (over 12 years of age) attending the Groote Schuur Hospital in Cape Town during the years 1952 to 1956. The patients included three segments of the population: the white, the Cape colored (comparable to the American Negro) and the Bantu. Electrocardiographic evidence of coronary vascular disease was rare in the Bantu, being present in only 3 patients. By contrast, the electrocardiographic evidence of coronary arterial disease was found more commonly in white than in the Cape colored (3 to 1 ratio). Such a disproportionate incidence was found in all age groups beyond the age of 30 years. This difference was not due to differences in age distribution. The incidence was considerably higher in males than in females. No coronary artery disease was encountered in the Bantu female.

Schrire and Uys[196] also studied the incidence of coronary artery disease in necropsy records in Cape Town. During the years 1952 to 1956 there were 1,651 necropsies (11% Bantu, 43% Cape colored, and 45% white). Despite the greater number of non-white, it was noted that there were 119 instances of myocardial infarction in whites and 43 in Cape colored. There were only 2 cases on record in the Pathology Department of the Groote Schuur Hospital of infarction in the Bantu, and in neither of these was there evidence of coronary atheroma. Infarction was associated with malignant hypertension in one patient and with syphilis in the other. They found the record of only one Bantu patient with infarction due to coronary atheroma. This was a Bantu male necropsied at the Government Medical Legal Laboratory.

The above races in South Africa are

genetically distinct. The whites are mainly descendants of immigrants of Great Britain and Holland[194]. The two main population groups in Africa are the Negro and the Bantu, the latter having arisen from a modification of the predominantly Negro race by Hamitic influence. The Negro migrations into West Africa were free from Hamitic influence and, presumably, it is from this group that the Negroes of the United States are derived. The Cape colored people in the Union of South Africa are derived mainly from the original Hottentot inhabitants with a considerable admixture of slaves brought from Indonesia and Malaya and also with promiscuous whites[27]. The Cape colored of South Africa are similar to the American Negro rather than the Bantu. It should be realized, however, that important anthropological differences do exist between the West African Negro people (from whom the American Negroes descended) and the South African Negro people. An important example of the difference is the rarity of sickle cell hemoglobin in the South African Negro as opposed to the West African and American Negro[115].

The data above are in general agreement with other reports from Africa of the rarity of coronary thrombosis in the Bantu in Cape Town[27,194,196,228]. A similar low incidence of myocardial infarction in the Bantu population of Johannesburg has also been reported[11, 14,15,52,92]. Gelfand[62] encountered no case of coronary heart disease in Southern Rhodesia in 15,000 consecutive admissions to a Bantu hospital over a one and one-half year period. Davies[39] reported the extreme rarity of coronary thrombosis in Negroes in Uganda. He had not at that time ever seen an instance of infarction in East Africa confirmed by necropsy. A comparable low incidence of cardiac infarction has been recorded by Edington[51] in the West African Negro.

Again, it must be emphasized that atherosclerosis must not be equated with coronary thrombosis. Evidence is accumulating to show that cerebral and peripheral vascular atherosclerosis may not be infrequent in the South African even though the incidence of coronary thrombosis is low[161,231].

2. *Metabolic Aspects of Arteriosclerosis.* Most of the data concerned with diet and lipid metabolism in the Negroes have originated from South Africa. This interest is related to the extraordinary low incidence of coronary occlusion in the Bantu[27,43,90,92,120, 121,194,196,229]. The Bantus receive only 16% of their total calories from fats, as compared to 25% for the Cape colored and 40% for the African Europeans. The latter have diets comparable to Northern Europeans and Americans. Paper electrophoresis showed that beta lipoproteins in Bantus averaged 52% of that in Europeans of the same age, the Negroes being intermediate. Serum cholesterol averages for men of 47 years of age showed 166.2 mg. per 100 ml. for 113 Bantus, 202.5% for 93 Cape colored and 250.1 mg. per 100 ml. for 57 "Europeans"[120]. A direct relationship between body fatness and serum cholesterol was marked in the Bantu, slight in the Negro, and absent in the European[157].

Tejada *et al.*[218] noted that there was an apparent correspondence between the dietary fat intake, serum cholesterol levels, S_f 0–12 lipoprotein patterns, and the degree of aortic atherosclerosis for people of Costa Rica, Guatemala and New Orleans.

C. RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE. Diehl *et al.*[45] recently reviewed epidemiology in rheumatic fever. It is extremely difficult to evaluate racial differences in rheumatic disease, since many factors other than

race play a part. Socioeconomic and environmental differences are particularly important. Other variables such as distribution of the races, differences in investigative technique (clinical versus necropsy) and differences in diagnostic criteria must be considered. In spite of these difficulties racial differences apparently do exist. In a pediatric clinic in Philadelphia where the white and Negro distribution was approximately equal, Ash[6] found that 83% of the patients with rheumatic fever were white, whereas 17% were Negro. She also found that once the Negro developed rheumatic fever he did not tend to do as well as the white and the Negro also had more frequent and more severe residual heart involvement. Hedley[83,84] also from Philadelphia, noted that the peak of the initial attack rate for Negroes was between the tenth and fourteenth years, whereas that for the whites was between the fifth and ninth years. The death rates for rheumatic fever and rheumatic heart disease were higher in the Negro than in the white for both the North and the South[45,83,84]. Almost all authors with clinical and necropsy data reported the incidence of rheumatic fever to be greater in the white race than in the Negro in a ratio of slightly less than 2:1[31,40,45,59,82,98,99,103,125,132,172,173,192,197,199,213,248]. Not every series is in full agreement, however. Wedum and Wedum[233] found in Cincinnati that the Negro had a higher incidence of rheumatic fever than the whites. In agreement with other reports, however, they were of the opinion that the disease was more severe in Negroes than in whites.

Because of great difficulty in controlling socioeconomic and environmental factors, Vesey[226] studied the epidemiology of rheumatic fever in a military establishment and military hospital. At one of the nation's large training camps during the years 1944 to 1945, 269,917 men were processed. Of this group 212,776 were white, and 57,141 were Negro. The men were housed in the same buildings, had the same food and clothing, and underwent the same type of training, fatigue, and environmental exposure. From this total group during those 2 years, there were 435 instances of rheumatic fever, an incidence of approximately 0.2%. Of these 435 patients, 395 were white and 40 were Negro, an incidence of 0.181% for the whites, 0.07% for the Negro, or more than twice as high in the white as in the Negro. The Negro spent about 2 months longer than the white in recovering from his rheumatic fever, probably due to the greater severity of the disease in him. Organic heart disease following the acute attack was about 10% higher in the Negro than in the white. The incidence of rheumatic chorea has been a point of debate for many years, and is still unsettled. Most authors, however, found that although the chorea did occur in the Negro race, it was much less frequent than in the white[35,191].

The data from Africa relating to rheumatic fever and rheumatic heart disease are not clear. Becker[11,13] in Johannesburg and Gelfand[62] in Southern Rhodesia report that rheumatic fever is quite frequent, whereas Davies[39] in Uganda and Edington[51] on the West African Gold Coast indicate that it is infrequent or rare in Africans in those areas.

Thus, in summary, data in the English literature show a greater incidence of rheumatic fever in the white than in the Negro. There was a tendency, however, for the Negro, once he acquired rheumatic fever, to have a more severe course, to have more frequent residual heart damage, and to die at an earlier age. As a reminder, it must be pointed out that the opinions

above have been obtained mainly from studies in the Preantibiotic Era. Authentic information in comparable racial groups under the same socioeconomic and environmental conditions and on controlled prophylactic therapy, is not available.

D. INFECTIONS OF THE HEART. Considerable changes have been achieved in this field over the last two decades. This has been primarily the result of the influence of antibiotic agents, especially penicillin. The changes have been continuous and are still progressing.

1. *Syphilitic Heart Disease.* Due to its extreme prevalence in the preantibiotic era, incidence of syphilitic heart disease has decreased considerably. Because of decreasing importance, fewer studies relating to racial factors in syphilitic heart disease appear in recent literature. All reports have shown a greater incidence in the Negro both to syphilis and to syphilitic heart disease[8,21,31,33,40,48,71,96,102,106,109,110,113,125,131,143,153,159,172,197,213,223]. Because of considerable variations in reports of incidence, it is not possible to determine whether or not there has been a significant change in the white to Negro ratio over the last several years. The incidence of syphilis in the American Negro has been reported to vary from 12 to 74.1% in the preantibiotic era[110]. Most of the reports at that time showed an average incidence of recognizable cardiovascular syphilis of about 10% in the total number of patients with syphilis. At necropsy cardiovascular syphilis (especially aortitis) was found in 70 to 80% of all syphilitics[223]. The sex distribution of incidence consistently has been greatest in Negro males and next in Negro females. The sex distribution has not been so constant in the white race, most studies showing a greater frequency in the male, however[33,102,107].

All investigators agree that syphilitic heart disease was and still is more frequent in Negroes. The greatest source of debate has been related to the cause of this difference. Several reasons have been offered: (1) a greater frequency of the infection in the Negro[8]; (2) a true racial cardiovascular tissue susceptibility to syphilis in the Negro[109,132,146,153]; (3) less resistance to syphilis, since the Negro, being exposed to the disease a shorter time than the white, has had less time to develop resistance[132]; (4) different strains of spirochetes infect the Negro than the white[132]; (5) the Negro receives inadequate therapy compared to the white[223]; (6) the Negro is engaged in more strenuous occupations which load his cardiovascular system and predispose him to cardiovascular syphilis and more rapid progression of the disease[234]; and, (7) the Negro comes under medical observation at a more advanced stage of his disease[132,234]. However, no one theory or combination of theories yet has been satisfactory to explain the entire problem.

Little additional racial data and thoughts about the problem have been introduced by the reports emanating from Africa. Syphilis is an important problem there. It affects all races, and varies considerably from area to area[11,45,51,62,241].

Syphilis is decreasing rapidly for both races[71]. Hutcheson *et al.*[107] in 1953 reported that, notwithstanding 25 years previously syphilitic heart disease ranked among the three most frequent types of heart disease, by 1953 it constituted only 2.3% of all cases. Lee[126] in 1954 noted that the total cases of syphilis reported by the Public Health Service dropped from 575,593 in 1943, to 168,734 in 1952 and reported cases of primary and secondary syphilis after rising from 83,204 in 1943, to a peak of 106,539 in 1947, decreased

to 11,991 in 1952. White[239] remarked that cardiovascular syphilis by 1956 was responsible for less than 1% of all heart disease, whereas previously it produced nearly 25% of all cases. Cannon[32] reported in 1958 that within the few preceding years there had been a decline of approximately 75 to 90% in the number of fresh syphilitic infections reported throughout the United States and that the rates for lethal syphilitic lesions, as established by necropsy, had similarly declined.

2. *Tuberculosis of the Heart.* Much of what has been discussed for racial factors in syphilis applies to tuberculosis. Although large numbers of reports have been published concerning racial problems in tuberculosis in general, the data on tuberculous heart disease are scanty. Almost all general publications indicate a greater incidence, morbidity and mortality for tuberculosis in the Negro than in the white, both before and since the advent of chemotherapeutic agents[72,96,108,109,132,146,164,168,172,174,177]. The reasons advanced have varied. Probably the most frequently postulated cause has been that related to length of exposure of the two races to the disease and the lack of sufficient time for racial resistance to develop in the Negro. Tuberculosis is found to be more frequent, more severe, more progressive in its course, and more lethal in those people who have dealt with the disease a shorter length of time[132].

Pericarditis is the main cardiovascular manifestation of tuberculosis. Peery[172] reviewed the necropsy findings in 2,066 consecutive cases of which 518 deaths were due to cardiovascular disease (68 white and 450 Negro). There were 70 instances of "inflammatory" cardiovascular disease, 18 being of tuberculous pericarditis and all were in Negroes. In 1954 Goyette *et al.*[72] reviewed their findings in 27 cases of tuberculous pericarditis collected over the preceding 4 years at the Fitzsimmons Army Hospital. Sixteen cases (59%) were in Negroes. This was considered particularly significant since Negroes constituted only 10% of the armed forces.

Tuberculosis in Africans progresses more rapidly and is more lethal than in whites[132]. Tuberculous heart disease is a common problem in Africa producing approximately 5% of all forms of heart disease[11,39,51,62,242]. In 1954 Edington[51] reported that pericarditis occurred in 13.5% of patients with heart disease and that the pneumococcus and tubercle bacillus were the most common etiologic agents.

There has been a progressive decline in the rates of morbidity and especially of mortality for tuberculosis and tuberculous heart disease[32,239]. There has been a 90% reduction in the United States in the mortality rate, a decline from 194 per 100,000 population in 1900 to less than 20 per 100,000 in 1951[168]. As of 1953, however, tuberculosis mortality was still three and one half times as high in Negroes as among whites[168].

3. *Bacterial Endocarditis.* This is another disease in which the pattern has changed within the last several years because of therapeutic and prophylactic use of antibiotic agents[239]. Most of the racial data concerning endocarditis were accumulated during the preantibiotic era. A large percentage of reports in the preantibiotic era recorded a greater incidence of bacterial endocarditis in the white race[59,125,,132,172,213,219,220] with a white to Negro ratio varying from one and five-tenths to one[213] to seven to one[125].

Thayer[219,220] in 1926 and 1931 reviewed the problem of bacterial endocarditis of all types in 362 cases. The incidence in the white was greater than in the Negro for all forms of bac-

terial endocarditis except pneumococcal and gonorrheal. A report from Africa in 1931 showed the pneumococcus to be the etiologic organism in 8 of a total of 17 cases of acute bacterial endocarditis[242]. Hutcheson *et al.*[107] in 1953 in review of general incidence of heart disease noted that in 1,000 cases of organic heart disease (637 white and 363 Negro) bacterial endocarditis was present in only 4 (0.4%); 2 were white males and 2 white females. The lower incidence of bacterial endocarditis in the South[238] was considered a reflection of the lower incidence of rheumatic heart disease in the South.

Ruegsegger[188] in 1958 studied the problem of pneumococcal endocarditis and concluded that neither sex nor race seemed to have a predisposing influence on the incidence of the disease. It was noted that pneumonia was seen more frequently in the Negro but that the incidence of endocarditis was no greater among Negro than among white patients with pneumonia.

In summary, no definite reliable conclusions concerning racial factors in bacterial endocarditis can be reached. The apparent slightly increased overall incidence of the disease in whites is probably a manifestation of the increased incidence of rheumatic heart disease in that race and also possibly their greater incidence of congenital heart disease. The greater incidence of pneumococcal endocarditis in the Negro is probably a reflection only of the frequency of pneumonia in that race. The relatively high incidence of gonorrheal endocarditis in the Negro is probably a result of socioeconomic factors.

4. *Diphtheria and Diphtheritic Myocarditis.* Much has been written in the past concerning the relatively less susceptibility of Negroes to diphtheria[96, 97, 132]. The disease has been reported to be rare and mild in Africa[132]. Although Negroes generally have a lower net death rate from diphtheria than whites, they are found to have a higher diphtheria mortality in the first year of life and in adult life; only the age group from one to 16 years is relatively exempt from diphtheria[20, 122]. Because of better therapy and especially because of immunization procedures the above comments are becoming a matter of history. For example, in the Chicago Municipal Hospital in 1928 there were 1,009 admissions for diphtheria with a 16% death rate, whereas in 1948 there were only 8 admissions and no deaths[32].

E. CONGENITAL HEART DISEASE. The reported increase in incidence of congenital heart disease for both races over the last several decades and the apparent reasons for this change have been indicated in a preceding section. As cardiovascular diseases due to infection are yielding to newer therapies and other forms of heart disease are reducing in incidence, congenital heart disease has become relatively more frequent. An actual increase in total incidence is not the major factor, however. An increased awareness of congenital heart disease and newer diagnostic methods have uncovered cases previously missed. In addition, most of the studies of incidence of heart disease emanate from centers where cases of congenital heart disease have been referred for surgical correction.

Even though the changes noted above have occurred over the last two decades, some older data may still be useful in evaluating the incidence of congenital heart disease in the white and Negro. As seen in Table 1, of the combined total number of cases from six studies where the classification of congenital heart disease was listed, there were 2,060 white and 3,173 Negro cases of heart disease. Of these cases, congenital heart disease occurred

in approximately 2% of the white patients and approximately 1% of the Negro patients. In Table 2 obtained from a report in 1953, it can be seen that essentially the same ratio of two to one still existed, namely 9% of the whites and 4% for the Negroes. However, these data are difficult to accept, for it is impossible to believe that almost one of 10 white people with heart disease has a congenital cardiac lesion. Either the diagnosis of heart disease was not accurate or the data are extremely heavily biased. Such reports are responsible for the confusion existing in the medical literature.

In 1940 Murphy[157] reported a study on congenital malformations among deaths and stillbirths from all causes in Philadelphia over a 5-year period. It was noted that the white race had congenital defects in 57 per 10,000 live births while the Negro had only 32 per 10,000 live births. Thus, again there was the ratio of approximately two to one. Of all the congenital defects 8.6% were cardiovascular. The preponderance of congenital defects in the white race was confirmed by United States Government statistics dealing with birth, stillbirth, and infant mortality. Since pathological diagnoses were not always noted on the death certificate, data on specific cardiovascular defects are unreliable. From other sources a slightly higher incidence is recorded for general congenital malformations as well as congenital heart disease in the white than in the Negro[96,101,132]. Reliable data of specific congenital heart defects are not available.

Mongolism is frequently associated with congenital heart defects, especially AV communis. For many years it was said that this disease was extremely rare in the Negro, but more recent studies have shown that this is not so. Mongolism (with its associated defects) does occur in the Negro but probably not nearly as frequently as in the white[63,178,200,201].

One gains the impression from African literature that congenital heart disease occurs in natives with a frequency and distribution of specific types similar to that seen elsewhere in the world[11,12,51,62].

Thus, from the literature it would appear that the distribution of types of congenital cardiovascular disease is essentially the same in both the Negro and the white races but that the incidence of these defects is somewhat greater in whites by a ratio of approximately two to one.

F. SUBENDOCARDIAL FIBROELASTOSIS, ENDOMYOCARDIAL FIBROSIS, IDIOPATHIC CARDIAC HYPERTROPHY, LOEFFLER'S ENDOCARDITIS FIBROPLASTICA WITH EOSINOPHILIA, AND RELATED SYNDROMES. This is one of the most confusing fields of cardiology today. Terminology is diffuse, pathological reports conflicting and physiologic effects lacking. Such terms as endomyocardial fibrosis, subendocardial fibroelastosis, idiopathic cardiac hypertrophy, myocardosis, myocarditis, endomyocardial collagenosis, myocardial fibrosis, idiopathic congestive failure, nutritional heart disease other than beri-beri, idiopathic congestive failure with liver disease, fibroplastic endocarditis with and without eosinophilia, endocardial fibrosis, parietal endocarditis, idiopathic cardiomegaly, constrictive endocarditis, Loeffler's endocarditis fibroplastica and others, have all been used to describe cases with clinical and necropsy findings which are at least superficially similar. Confusion is always implied when so many closely related terms are introduced. Probably all of these syndromes have occurred in both white and Negro races and racial differentiation is not clear.

It is not the purpose of this discussion to attempt to clarify the above

problem or to describe the clinical picture. However, the following may be in order. In general the clinical syndromes consist of dilated or hypertrophied hearts, or both dilated and hypertrophied, usually with congestive failure, mechanismal disturbances, and mural thrombi with embolism. Response to various therapeutic procedures has been variable. At necropsy there have been described various combinations of the following: endocardial and subendocardial fibrosis (with and without extension into the myocardium and with and without proliferation of elastic tissue), myocardial fibrosis (patchy or diffuse), myocardial hypertrophy or dilatation, or both, and varying degrees of myocardial inflammation.

Obviously from all the confusion that exists with respect to the above diseases, it is not possible to draw any definite conclusions at the present time as to racial relationships. The following diseases probably have shown enough consistent differences to justify separate grouping. Their names indicate the basic pathological differences. It would appear that the syndrome of endomyocardial fibrosis occurs predominantly in Africa (especially East and West)[9,16,17,37,38,39,51,62,73,162,204]. Nutritional heart disease (non-beriberi) with similarities to endomyocardial fibrosis but with liver disease and good response to dietary therapy appears to be much more frequent in the South African Bantu[64,91]. Subendocardial fibroelastosis occurs over the world and has been recorded in both white and Negro races with variable frequency[37,46,139,141,166,176,186,222]. Idiopathic cardiac hypertrophy probably is more frequent in the Negro[54,130,131,211]. Loeffler's endocarditis fibroplastica with eosinophilia has been recorded over the world in both races[93,96]. Myocarditis will be discussed in a separate section.

G. PERICARDITIS. Most of the racial data available for pericarditis have been concerned with tuberculosis which was discussed above. Reliable and significant data for the other forms of pericarditis have not been available. Edington[51] in 1954 reported that pericarditis had accounted for 13.5% of all types of cardiovascular disease in Africa and that the pneumococcus and the tubercle bacillus were the most frequent etiologic bacterial agents. Africans are particularly susceptible to pneumococcal infection, and fulminating pneumococcal septicemia and meningitis are common causes of deaths in those people.

H. MYOCARDITIS. Racial aspects of diphtheria have been briefly discussed in a preceding section. Endomyocardial fibrosis and related syndromes sometimes confused clinically and pathologically with inflammatory myocarditis have also been discussed. Little information is available in the literature relating to racial factors for other varieties of myocarditis. Although no specific racial data were given, the impression gained from the large series reported by Saphir *et al.*[190] in 1944 and de la Chapelle and Kossmann[42] in 1954 is that myocarditis in general is relatively more frequent in the white race.

I. THYROID HEART DISEASE. Because of the conflicting reports from the literature, again it is difficult to arrive at any definite conclusions concerning thyrotoxicosis and thyrotoxic heart disease in whites and Negroes. The incidence of thyrotoxicosis in general in the United States is apparently similar for both races. The general mortality rate may be slightly higher in the Negro[22,143,245]. Thyrotoxic heart disease may be a relatively more frequent form of disease in the white than in the Negro as shown in Table 1 and elsewhere[59,107,125,132,213]. The preponderance of both thyrotoxicosis and thyrotoxic heart disease in the female in

both races has been noted[59,107,213]. At any rate, through earlier recognition and better therapeutic procedures, thyrotoxic heart disease is becoming a less important problem[107,238,239]. It is interesting that in reports from Africa on the incidence of the various etiologic types of heart disease, thyrotoxicosis is an extremely rare etiologic factor[11,51,62].

J. NEOPLASTIC CARDIOVASCULAR DISEASE. Multiple idiopathic hemorrhagic sarcoma of Kaposi has shown interesting racial differences. Several reports are available stressing the extreme rarity of this disease in the American Negro[53,115,138,214]. Hundreds of cases have been reported in the white race, but Syrop and Grantz[214] in 1951 were able to find reports of only 8 proven cases in the Negro. Of interest is the fact that this vascular neoplasm is a relatively common disease in Africa[86, 115]. Kaminer and Murray[115] in 1950 were able to collect 41 cases from the files of the South African Institute for Medical Research for the period of 1942 to 1949. Thirty-eight of these were in the South African Negro and only 3 were Europeans. Even though the Negro to white ratio of the general population in South Africa was 4:1, this would not account for the racial differences in incidence. Of the 38 cases in South Africans, 37 were males. Kaminer and Murray briefly discussed this contrast in incidence between the South African Negro and the American Negro and called attention to anthropological differences between the two groups.

K. SARCOIDOSIS OF THE HEART. Sarcoid involvement of the heart was reviewed by Arkless *et al.*[5] in 1958. Peacock *et al.*[170] collected 28 cases from the literature in which there was pathologic evidence of sarcoid involvement of the heart and added a case of their own. Arkless *et al.*[5] found 3 other cases from the literature plus another of their own, making a grand total of 33 cases in the literature. Of these 33 cases the race was known in 29, eleven being white and 18 Negro (8 white males, 3 white females, 10 colored males, and 8 colored females). The higher incidence in the Negro race is expected from the higher incidence of sarcoidosis in the Negro. The report of Arkless and others of 33 cases of myocardial involvement is difficult to understand since the heart is one of the organs frequently involved in sarcoidosis. The interest in racial incidence of cardiac involvement has been limited.

L. CARDIOVASCULAR DISEASE RELATED TO PREGNANCY. The racial incidence of eclampsia in the United States is essentially equal[7,77,152]. In a study from the Canal Zone, Scrimshaw[202] described significant differences in the racial distribution of toxic complications in pregnancy in the racial groups studied there. It was more frequent in Americans, next in Panamanians, and least in West Indian Negroes.

In 1937 Hull and Hafkesbring[104] and in 1938 Hull and Hidden[105] reported on a total of 54 cases showing the syndrome of "toxic postpartal heart disease" or "postpartal myocardial degeneration." These were patients who developed a dilated heart with congestive heart failure shortly after pregnancy in the absence of any known underlying etiology. The disease was more than twice as frequent in Negro patients as in white ones. Musser *et al.*[158] in 1938 and Melvin[148] in 1947, corroborated these racial findings in this syndrome.

Meyer[149] in 1938 reported a syndrome of "unexpected postpartum hypertension" occurring after a normal pregnancy in a previously normal patient. This study included 490 patients examined at a routine 6-weeks postpartum visit. It included 279 whites and 211 Negroes. Of this group the syndrome was found in 23 patients and

all were Negresses. In 1941 Meyer and and Nadler[150] again discussed this syndrome and added an additional 28 patients and again all were Negresses. The etiology of this disease remains unknown. This syndrome appears to be related to or is a variant of the postpartal heart disease described in the preceding paragraph.

M. MISCELLANEOUS. *1. Arrhythmias.* A few studies have appeared in the older literature dealing with the racial differences of cardiac arrhythmias. Except for the Wolfe-Parkinson-White syndrome, only atrial fibrillation has been shown to have any consistent racial difference and the statistical significance of this is not clearly established. In 1937 Flaxman[58] studied 623 cases of hypertensive heart disease and found the incidence of atrial fibrillation to be 32.3% in whites and 9.8% in Negroes. In cases of essential hypertension Weiss and Prusmack[237] in 1938 confirmed the higher incidence of atrial fibrillation in the white patients than in the Negroes.

Garvin[60] in 1942 studied 790 consecutive patients who died of heart disease. In a group with arterial hypertension, the incidence of atrial fibrillation was 23.8% in whites and 17.7% in Negroes. In the patients with coronary heart disease (158 whites and 19 Negroes) the incidence of fibrillation was 21.5% in whites and 5.2% in Negroes. In patients with rheumatic heart disease (103 whites and 16 Negroes) fibrillation was found in 55.3% of the whites and 31.2% of the Negroes.

2. Anemic Heart Disease. As indicated previously, anemic heart disease is probably far more frequent, especially in its more subtle forms, than would appear from the incidence of the various etiologic types of heart disease reported in the medical literature. The racial incidence of this disease would be expected to reflect the distribution of different specific anemias among the racial groups. For example, pernicious anemia is relatively infrequent in the Negro race[132,247] whereas sickle cell disease is practically limited to the Negro race. With respect to sickle cell disease, Winsor and Burch[246] found that during a single year, 1941 to 1942, there were 40 patients with this disease recognized on the wards of Charity Hospital in New Orleans. Of this group, the great majority had heart disease.

Anemic heart disease is a common problem in Africa and the tropical and poorer areas of the world. Gelfand[62] in 1952 reported that it comprised 5.8% of all cases of heart disease in Africans.

3. Atrophy of the Heart. In 1950 Hellerstein *et al.*[86] reported a study of 85 cases of cardiac atrophy encountered in 200 consecutive necropsies. It was noted that cardiac atrophy occurred in conjunction with a variety of diseases, most important of which were neoplasms (73%) and chronic infection (16%). Seventy of the cases were white and 15 were Negroes, a ratio of 4.7:1. This racial difference was not significant when correction was made for the 4:1 racial ratio in the total necropsy population. After suitable corrections were made for total necropsy population, the ratio of females to males was 3:1.

4. Amyloidosis of the Heart. In 1939 Koletsky and Stecher[122] reviewed the problem of primary systemic amyloidosis which usually involves the heart as well as the gastrointestinal tract and skeletal muscle. They reported a patient of their own in whom there was extensive amyloid infiltration of the valves of the heart. It was noted that at the time of their study there were 23 reported cases in the world's literature of primary systemic amyloidosis and all were in the white race.

5. The Heart in Von Gierke's Disease.

Von Gierke's disease almost invariably involves the heart. Tolmas[224] in 1950 reported a case of this disease in a Negro infant. This is the only such case in a Negro that could be found in the literature up to that time.

6. Racial Aspects of the Electrocardiogram. Most of the discussion in the literature concerning racial variations in the electrocardiogram has dealt with the so-called "persistence of the juvenile pattern" manifested primarily by inverted T waves in the anterior chest leads. Several studies have shown a significantly increased incidence of such negative T waves in the Negro race[24, 67,76,137,232]. Others have found in general no consistent difference in the electrocardiograms of the two races[8, 118]. The problem is as yet unsettled and the difficulty probably lies in the evaluation and control of such factors as electrode placement, heart position and associated diseases.

That the electrocardiographic syndrome of the short PR interval and broad QRS complexes (WPW syndrome) occurs significantly more frequently in the white race appears conclusive[85]. The racial incidence of atrial fibrillation has been discussed in a preceding section.

7. Diseases of the Peripheral Vessels and the Collagen Vascular Disease. Accurate racial data concerning the peripheral manifestations of arteriosclerosis have not been available. There is a suggestion that the Negro develops arteriosclerotic gangrene at an earlier age and suffers a higher mortality rate from this disease than do white people[143]. It is generally accepted that intracranial lesions of a vascular origin (including arteriosclerosis) have a higher incidence in the Negro race[11,14,15,27,51, 71,90,92,124,132,174,189,196,237]. This is of considerable interest in view of the relatively lower incidence of coronary artery disease in the Negro.

Much has been written concerning the rarity of thromboangiitis obliterans in the Negro. However, several case reports of this disease in Negroes have been reported[23,39a,61,114,132,167,209,231,249]. Gemmill[61] in 1926 apparently reported the first case in a Negro. Johnston[114] reviewed the literature on this disease in 1953 and found 10 clinically and histologically proven cases of thromboangiitis obliterans in the Negro race. Only one of all of the patients could have been considered a full-blooded Negro and only one of the patients was a female. Johnston commented on the presence of white ancestry in most of the reported Negro cases, on the frequency of associated lues, and on the rapid progression of the disease in the Negro once it developed.

It appears that disseminated lupus erythematosus (as opposed to older views) occurs with equal frequency in both races[49,80,111] while periarteritis nodosa occurs with a white to Negro ratio of approximately 3:1[161]. Hereditary hemorrhagic telangiectasia and its associated pulmonary arteriovenous fistulae is extremely more frequent in the white race[55,68,156,160,163,185,208,210, 221,250]. Temporal arteritis is extremely rare in the Negro[18]. A rare syndrome of generalized fibrosis and hyperplasia of the media of the arterial system has been described only in the Negro[179, 251]. Vascular injuries due to cold have been found to be significantly more frequent in the Negro than in the white race[147] under similar environmental conditions. The disease, ainhum, is for all practical purposes, limited to the Negro races[28].

CLOSING COMMENTS. This review summarizes briefly an extensive study of the literature on the racial differences in incidence of cardiovascular disease. Most of the published studies have not been carefully conducted. An effort was made to point out deficien-

cies in these studies and to eliminate the less critical ones. The need for careful and well-planned investigations of cardiovascular disease in Negroes and whites is evident. Because of the limitations present in the reviewed literature, it is impossible to arrive at any absolute values and, therefore, only trends in the racial differences in incidence can be given. Although the degree of these differences in cardiovascular disease varies considerably, the direction of the trends has been remarkably similar in numerous reports. Several reasons for these raeial variations can be cited. It appears that many racial differences reflect not only genetic and racial factors but variations in the medical care available and extended to the Negro, and the Negro's cooperation and participation in this medical care.

The racial incidence of cardiovascular disease has changed considerably since the advent of antibiotic agents. This change has been so marked that the incidence during the preantibiotic era must be considered a phase of the history of medicine. The role of such data in present day cardiovascular medicine is that of history and its importance lies in its influence on future courses and predictions.

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BOOK REVIEWS AND NOTICES

PATHOPHYSIOLOGY IN SURGERY. By JAMES D. HARDY, M.D., F.A.C.S., Professor of Surgery, University of Mississippi Medical Center. Pp. 704; 278 ills. Baltimore: The Williams & Wilkins Company, 1958. Price, $19.00.

THE author of this book is to be congratulated on the thoroughness with which he has covered the various topics of surgical importance and yet managed to be concise. The first ten chapters deal with basic considerations of injury and repair, fluid and electrolyte metabolism, nutrition, infection, burns, enzymology, and radiology. Following this, each system is considered from the viewpoint of its normal physiology and the aberrations occurring with various disease states.

Clinical material is used effectively to illustrate facts and concepts, but all technical detail is deleted. There are excellent sections on anesthesia, the endocrine system, the nervous system, and special pediatric problems as well as the expected considerations of the gastrointestinal, cardiovascular, and respiratory systems.

The single authorship makes for a continuity of thought and viewpoint, which enhances digestion of a large volume of factual material. The reviewer would suggest that this book be required reading for any surgical trainee and would recommend it highly to any surgeon as a timely review of the basic science of surgery. R.B.

CHEMOTHERAPY AND THE CENTRAL NERVOUS SYSTEM. By HENRY MCILWAIN, PH.D., D.SC., Professor of Biochemistry, University of London. Pp. 328; 61 ills. Boston: Little, Brown & Co., 1957. Price, $10.00.

THIS book deals with the chemotherapeutic approach to the problems of nervous, mental, and emotional disorders. The discussions have a basic orientation. Chapters are devoted to chemical synthesis of therapeutic agents, general depressants, and the thermoregulatory mechanism. There are full discussions of the bodily distribution and metabolism of drugs, of specific anti-infectious agents, of anticonvulsants, analgesics, excitants, and depressants. In addition, there is an excellent section on metabolic and biologic antagonism and the application of these interrelationships to disturbances of the central nervous system. The final chapter is devoted to a consideration of the nature and results of chemotherapeutic experiments.

Neurophysiologists, neuropharmacologists and clinical neurologists and psychiatrists who are involved in research in these areas will find this a worthwhile volume. C.Z.

BIOCHEMISTRY. By ABRAHAM CANTAROW, M.D., Professor of Biochemistry, AND BERNARD SCHEPARTZ, PH.D., Assistant Professor of Biochemistry, Jefferson Medical College. 2nd ed. Pp. 867; 150 ills. Philadelphia: W. B. Saunders Co., 1957. Price, $12.00.

THIS is a revision of what has proven to be one of the best textbooks on Biochemistry available in the English language. While every chapter has been revised in order to bring the factual information up-to-date, the authors have maintained the lucid and readable style for which they are noted. Among the topics regarding which new data have been included are: adrenocortical, thyroid and hypothalamic hormones; structures of insulin, vasopressin, and oxytocin; metabolic and nutritional significance of trace elements; neurochemistry; the relation of folic acid and tetrahydrofolic acids and B_{12} to the metabolism of 1-carbon fragments; and lipoproteins.

As before, physicochemical concepts are considered in their direct relation to biochemical phenomena. Another valuable feature is the effort of the authors to indicate those areas of investigation where recent observations seem to foreshadow future advances.

For students in biochemistry, as well as for physicians desiring a contemporary reference text on the subject, this volume is highly recommended. C.Z.

CLINICAL ENZYMOLOGY. Edited by GUSTAV J. MARTIN, SC.D., Research Director, National Drug Company, Philadelphia. Pp. 241; 15 ills., 8 in color. Boston: Little, Brown & Co., 1958. Price, $6.00.

THE basic knowledge necessary to an understanding of clinical enzymology is outlined in this volume. Included are discussions of Protein Biology, the Chemistry and Biochemistry of Enzymes Used Clinically, the Parenteral Use of Enzymes in Medicine, the Diagnostic Use of Enzymes, and Polymerases in

Biology. The final chapter recapitulates the current status of the field and offers some interesting observations regarding perspectives for clinical enzymology.

Physicians will find this an informative and readable book on a biochemical area of rapidly increasing clinical importance.

C.Z.

Les Déchirures: Obstétricales, Compliquées, Du Périnée Traitement Chirurgical. By Rene Musset, Marcel Cottrell, and Maurice Dubost. Pp. 118; 21 ills. Paris: Masson et Cie, 1958. Price, 1.400 fr.

This monograph presents a complete review of severe obstetric perineal injuries. The authors have reviewed the literature and, as well, have presentd their own techniques for correcting these lesions. One chapter is devoted to an extensive historical survey in which the development of present day operations is traced. The remainder of the book is concerned with the etiology, recognition and management of perineal lacerations.

They state that about 30% of the injuries occur because of poor obstetric technique and the remainder because of constitutional anomalies which include infantile genitals and short perineum. Preventive measures are described. The operative correction of both acute and chronic injuries is described and illustrated in detail and preoperative preparation and postoperative care are discussed.

The monograph adds little that is new but because of its historical survey and the extensive bibliography it should prove useful as a reference for those interested in the study of perineal injury. J.W.

Advances in Clinical Chemistry, Volume 1. Edited by Harry Sobotka, Department of Chemistry, Mount Sinai Hospital, New York, and C. P. Stewart, Department of Clinical Chemistry, University of Edinburgh. Pp. 398; illustrated. New York: Academic Press, Inc., 1958. Price, $12.00.

This volume initiates a new series of publications which should prove invaluable by its presentation of timely, authoritative discussions of newer methods in clinical chemistry. For example, the first volume offers excellent dissertations on Plasma Iron; the Assessment of Tubular Function of the Kidneys; Protein-Bound Iodine; Blood Plasma Levels of Radioactive Iodine-131 in the Diagnosis of Hyperthyroidism; Determination of Individual Adrenocortical Steroids; the 5-Hydroxyindoles; and the Clinical Significance of Alterations in Transaminase Activities of Serum and Other Body Fluids. There are also valuable sections on Paper Electrophoresis of Proteins and Protein-Bound Substances in Clinical Investigations, and on the Composition of Body Fluids in Childhood.

All clinical investigators and clinical pathologists will wish to have this volume as well as its projected successors if the high level of excellence is maintained. C.Z.

Schizophrenia. By Manfred Sakel, M.D. Pp. 335; 1 ill. New York: Philosophical Library, Inc., 1958. Price, $5.00.

The late Dr. Manfred Sakel was the discoverer of insulin shock treatment which for a time was the mainstay in the treatment of schizophrenia. This treatment helped to dispel the therapeutic nihilism that previously existed toward schizophrenia. In the second half of this book, Dr. Sakel describes the discovery of insulin shock in 1927, and its theory and clinical application. The first half of the book describes schizophrenia in chapters on man and his mind, classification, etiology, method of examination, symptomatology, general psychopathology, postmortem findings, prognosis and paranoia. Dr. Sakel believes that his insulin shock treatment has proved beyond doubt that the cause of schizophrenia is pathophysiological. However, in the past few years many psychiatrists have questioned the effectiveness of insulin shock and its use has been declining.

Since Dr. Sakel takes for granted the somatic etiology of schizophrenia he gives only cursory coverage to its psychodynamics and psychopathology. Also he discusses no therapy other than insulin. There is no bibliography. The book is not comprehensive enough to be recommended as a textbook on schizophrenia. However, it is a valuable and authoritative exposition of insulin shock treatment. L.A.

The Reproductive Development of the Female. By M. F. Ashley Montagu. Pp. 234; 4 ills. New York: The Julian Press, Inc., 1957. Price, $5.00.

This book brings up-to-date the subject of adolescent sterility, in which the author has been interested for many years and on which he has written previously. He, as well as other anthropologists, had observed that in primitive peoples with complete sexual freedom few babies were born to unmarried girls

and to those recently married if the marriage ceremony were performed during early puberty. In human beings the adolescent sterility period varies between one month and seven years. Similar periods of infertility have been observed in other mammals.

From an endocrinologic point of view this can be explained by the fact that the first menstrual periods are anovulatory making conception impossible. In addition infant loss from early abortion, fetal death and neonatal death is high. The author attributes this in part to inadequate pituitary activity and thus, inadequate pregnancy hormone production. He suggests the following divisions of female development: *Adolescent Sterility Period*, 13 to 16 ± 1 year; *Nubility*, 17 to 22 ± 2 years, during which time conception may occur but infant loss is high and *Maturity*, 23 to 28 ± 2 years. The most favorable period for reproduction, with respect to this he makes an interesting and undoubtedly an unenforcible suggestion, ". . . The society that would be healthy would do well to consider these facts, and raise the age of marriage for the female accordingly."

His ideas are extensively documented by recent publications, but also by papers published during the last century. His conclusions concerning infant and maternal mortality trends undoubtedly are correct but they would be far more convincing if he had used current information on vital statistics rather than those between 1922 and 1936. His conclusion that the poor result of endocrine and sexual immaturity are open to question unless the other factors of social economic status, prenatal and hospital care, and the like, are also considered.

The mass of statistics makes this volume a little difficult to read and it undoubtedly will not be consumed on a popular level. It should, however, prove valuable as a reference to those interested in the study of anthropology and population problems.

J.W.

Physical examination of the surgical Patient. By J. Englebert Dunphy, M.D., Professor of Surgery, and Thomas W. Botsford, M.D., Clinical Associate in Surgery, Harvard Medical School. 2nd ed. Pp. 375; 203 ills. Philadelphia: W. B. Saunders Co., 1958. Price, $8.00.

As was true of the first edition of this book, it has not been written to cover all of physical diagnosis, but rather supplements these texts by considering and emphasizing those factors which are of importance in the surgical patient. The first part covers the general physical examination, and the second part considers the emergency examination in trauma. This second part in itself makes the volume quite valuable.

The text is well illustrated with clinical pictures and diagrams. The reviewer recommends this book to the medical student and the surgical student as much more important than any manual of normal and abnormal laboratory values.

R.B.

Nutrition and Atherosclerosis. By Louis N. Katz, M.D., Director, Cardiovascular Department, Medical Research Institute Michael Reese Hospital, Jeremiah Stamler, M.D., Director Heart Disease Control Program, Chicago Board of Health, and Ruth Pick, M.D., Assistant Director, Cardiovascular Department, Medical Research Institute Michael Reese Hospital. Pp. 146; 67 ills. Philadelphia; Lea & Febiger, 1958. Price, $5.00.

Those who enjoyed the excellent book, Experimental Atherosclerosis, by Drs. Katz and Stamler, published in 1953, will be delighted to know that this new volume constitutes an extensive review of the literature since that time with particular emphasis upon nutritional aspects. The bibliography contains 787 references and this alone is enough to warrant an excellent recommendation. Five chapters of the text deal with the current status of understanding of nutritional factors in atherosclerotic disease, and these along with one which covers hormonal and other endogenous factors, set the stage for the closing chapter which presents a definitive approach to prophylaxis and therapy in man. The authors believe that "the cornerstone of modern therapy for patients with coronary disease today seems to be an increasingly scientific dietary prescription aimed at correcting the nutritional-metabolic derangements intensifying atherogeneses." For persons not yet victimized by clinical coronary disease they believe that there is "one sizeable segment of the American population particularly in need of prophylactic advice from the medical profession." A program is presented which is not limited entirely to dietary advice. While some cardiovascular experts will disagree with these conclusions, the size of the dissident group has been rapidly decreasing in recent years, and it the strong conviction of the reviewer that the recommendations should be heeded.

T.D.

CARDIOVASCULAR SOUND IN HEALTH AND DISEASE. By VICTOR A. MCKUSICK, M.D., Associate Professor of Medicine, The Johns Hopkins University School of Medicine. Pp. 570; 494 ills. Baltimore: The Williams & Wilkins Co., 1958. Price, $15.00.

IT is extremely difficult to avoid using superlatives in reviewing this book. It is so excellent in every respect and so practical that it should be read and reread by every internist and general practitioner. As stated in the preface, "Cardiovascular sound and cardiac auscultation are at the hub of clinical cardiology and cardiovascular physiology," and an exhaustive treatise on these subjects does indeed "approach being a textbook of cardiology." Though illustrated throughout by spectral phonocardiography, a technique which may not become generally available for some years, the physician can readily translate the presentation into a far better understanding of what he hears at the bedside, particularly since he will be given an understanding of the physiology and pathophysiology involved. It is to be hoped that the book will be effective in counteracting the present day trend toward emphasis upon electrocardiography, angiocardiography, and other machine techniques at the expense of the mastery of physical diagnosis. It should be added that the well trained cardiologist also will find the book of great value since the recent literature has been carefully reviewed and there is a list of 1607 references. An excellent appendix provides important data concerning spectral phonocardiography and other technical matters relating to the recording and storing of heart sound information.

T.D.

THERAPEUTIC EXERCISE. Edited by SIDNEY LICHT, M.D., Assistant Clinical Professor of Medicine (Physical Medicine), Yale University School of Medicine. Pp. 893; 204 ills. New Haven, Conn.: Elizabeth Licht, 1958. Price, $16.00.

THE third volume of "Physical Medicine Library" entitled THERAPEUTIC EXERCISE is to date the most formidable and complete work in this series being published under the scholarly editorship of Sidney Licht. This book is little short of encyclopedic in scope. There is ample justification for bringing out such a volume since it deals with the most important and presently most popular field of physical medicine. This is the first successful attempt in a century to cover adequately in a single volume the entire expanding and complicated field of remedial exercise in health and in disease; an area too long overlooked by the majority of the medical profession.

The Editor, realizing that no one individual is capable of discussing satisfactorily a subject of such wide range, wisely distributed the task among 36 physicians, all recognized as preeminent in their special fields. It is noteworthy that one-third of the authors are outstanding investigators or clinicians from European countries. Thus, the reader is presented with a group of authoritative essays which cover essentially every aspect of exercise. It is a tribute to careful editorial supervision that in spite of the diversity of authorship, there is a gratifying uniformity in the literary style and presentation throughout the text.

The physiological fundamentals which underlie all exercise are considered in the first half of the book which includes chapters on the Motor Unit, the Physiology of Exercise and Fatigue and the Mechanical Anatomy of Motion and Posture. Then follow discussions of commonly performed motions, muscle and joint movements, manual muscle examination and five chapters on the most often used types of exercise. This arrangement emphasizes the close relationship of basic science to the clinical considerations of exercise which follows.

An innovation is the introduction of a chapter on the therapeutic gymnasium which includes a floor plan as well as a description of mechanical devices and apparatus of proved usefulness in exercise programs. Mention must also be made of the sections on Kinetic Occupational Therapy, the Place of Sports in Medicine and the Use of Crutch and Cane Exercises.

Midway through the volume the Editor has prepared a highly informative and interesting account of a History of Therapeutic Exercise as broadly considered.

The remainder of the book is devoted to considerations of exercise in a variety of diseases and disabilities, for example poliomyelitis, arthritis, hemiplegia and other neuromuscular disorders. The concluding chapters deal with conditions that belong to the various specialties, such as orthopedics, psychiatry, ophthalmology and obstetrics as well as cardiovascular and pulmonary disease. The final section presents the useful and often neglected subject of exercise of healthy persons of all ages.

In order to insure completeness, there are two appendices, one in which brief isometric exercises are discussed and the other, prepared by the Editor, includes a miscellaneous

group of other exercises arranged alphabetically which are not emphasized in the main chapters.

The illustrations, which number 204, are informative and helpful. The authors and subject indices are carefully prepared and satisfactory. The publishers are to be commended on the appearance of this volume and the excellent typographical composition.

This book is highly recommended to every practicing physician, regardless of his chief interest, who will find it the most complete and useful text available in English on a subject of increasing medical importance.

G.P.

PSYCHOSOMATIC OPHTHALMOLOGYY BY T. F. SCHLAEGEL, JR., M.D., Assistant Professor of Ophthalmology, Indiana University School of Medicine. Pp. 523. Baltimore: The Williams & Wilkins Company, 1957. Price, $11.00.

THE psychosomatic aspect of eye problems is included in many of the books of ophthalmology for the sake of completeness or as an afterthought. This is the most complete guide to a basic understanding of the role emotions play in ophthalmology.

This book is in keeping with the realization of all medical authors that the psychosomatic aspects of disease can no longer be ignored. The physician who is unaware of what he cannot see faces needless confusion, daily.

You may not agree with the author; you may feel that the functional has been overemphasized; but if you start to read this thought-provoking book it will prove to be beneficial and easy to take in large or small doses.

L.H.

DISINFECTION AND STERILIZATION. BY G. SYKES, M.SC. (LOND.), F.R.I.C., Standards Department, Boots Pure Drug Co., Ltd., Nottingham. With a Foreword by G. S. WILSON, M.D. Pp. 396; 7 ills. Princeton: D. Van Nostrand Co., 1958. Price, $10.75.

IN a short book of only 17 chapters, the author, who has over 30 years industrial bacteriology experience, evaluates most of the information available today concerning sterilization, disinfection and preservation. With British clarity and precision, an historical review is followed by discussions of methods of testing disinfectants and antiseptics; sterilization by heat, radiation, filtration and gases; air disinfection and sterilization; and disinfection of viruses. One of the six parts of the book is devoted to the phenolics, alcohols, dyes, "quats," halogens, and heavy metals. The last part concerns preservation of various industrial and pharmaceutical products.

The author has drawn heavily on both the British and American literature and clearly cites references for all statements. Over 1000 references are listed both in an author index and at the end of appropriate chapters. Comparisons are frequently drawn between practices employed in the United States and Great Britain. The fallacy of phenol coefficients is frequently pointed out along with the extravagance of claims made for some compounds. There is no mention of the use of beta propiolactone for graft sterilization or possible enclosed-space disinfection, nor is there much discussion of residual acting germicides.

The book should be of value to physicians, nurses and microbiologists and impart to them a clear understanding of the concepts of disinfection and sterilization.

K.S.

COLLECTED PAPERS: THROUGH PAEDIATRICS TO PSYCHOANALYSIS. BY D. W. WINNICOTT, F.R.C.P. (LOND.), Paddington Green Children's Hospital, London. Pp. 350; 20 ill. New York: Basic Books Inc., 1958. Price, $6.50.

THE contents are selected papers, arranged in three sections, that span 35 years of practice in the combined medical specialities of pediatrics and psychoanalysis.

Clinical papers comprising the first two sections demonstrate the wealth of psychological data available from direct contact with children and the value derived from the application of psychoanalytic principles to the therapeutic programs.

The final section, comprising two-thirds of the book, contains some of the author's views about psychoanalytic theory and practice. These views coincide generally with those of Melanie Klein. Since knowledge of psychoanalytic theory is a prerequisite for proper evaluation of these views, this book is not addressed to beginning students of medical psychology.

W.R.

DIFFERENTIALDIAGNOSE NEUROLOGISCHER KRANKHEITSBILDER. BY PROFESSOR G. BODECHTEL. Pp. 975; 532 ills. Stuttgart: Georg Thieme, 1958 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, DM 120. ($28.60).

THIS volume, concerned entirely with the differential diagnosis of nervous diseases, is a comprehensive survey of diagnosis, not of symptoms, but of diseases, with particular reference to their pathogenesis. It is beautifully and abundantly illustrated, and in all categories is complete and current.

Most of the chapters are in reality small monographs of special problems such as those relating to diseases of the peripheral nervous system, circulatory disturbances of the brain and spinal cord, inflammatory diseases of the nervous system, and tumors. The chapter on the peripheral nervous system is especially well done, but the others are of a similar high quality. There is a particularly instructive chapter on cerebral intoxications which is extremely comprehensive.

It is somewhat surprising to find multiple sclerosis discussed with inflammatory diseases of the nervous system and neurosyphilis. Parkinsonism is found included in the chapter of metabolic diseases of the nervous system, but here an effort is made to avoid use of the term degenerations and to prefer dystrophic processes in its stead. The problem of seizures and epilepsy receives less attention than it merits, but there are good discussions of headache and unconsciousness.

The volume is outstanding as a discussion of neurological diagnosis and can be highly recommended to all neurologists. B.A.

THE CHEMICAL PREVENTION OF CARDIAC NECROSIS. BY HANS SELYE, M.D., PH.D., D.SC., Professor and Director of Experimental Medicine and Surgery, University of Montreal. Pp. 235; 20 ills., 1 color plate. New York: The Ronald Press Company, 1958. Price, $7.50.

SELYE presents herein a brilliant and startlingly new concept of the pathogenesis of cardiac necrosis based upon the knowledge that hormones are capable of altering the reactivity of the body so that otherwise innocuous agents become harmful and produce morbid change. He has found that combined treatment with certain electrolytes (E) and steroids (S) produces a cardiopathy (C) characterized by necrosis (N). Thus, the label "ESCN" is derived.

ESCN was produced by only certain sodium salts following conditioning with steroids. Phosphates, sulfates and perchlorates were particularly effective while chlorides, nitrates, permanganates and most of the organic salts were inactive. Also, only some corticoids were able to condition the heart. Pure glucocorticoids were ineffective whereas 2 alpha methyl 9 alpha chlorocortisal possessed the highest potency.

Following such treatment, necrotic foci appeared anywhere within the myocardium and particularly in the right ventricle, atria and subendocardium of the left ventricle. Initially, there occurs "fuchsinophilic degeneration" and necrosis of single muscle fibers which, if large enough, is followed by cellular infiltration and scar formation. The cardiopathy so produced is prevented by potassium or magnesium chloride.

These observations lead Selye to believe that a labile chemical system exists within the myocardium which can be easily deranged by some metabolic effect of stress acting in the presence of hypercorticoidism and an excess of sensitizing sodium salts. Thus, the clinical "necrotizing cardiopathies," elicited by a host of agents and characterized histologically by first necrosis, then inflammation and finally fibrosis, are reduced to a common pathogenesis. J.Z.

THE PSYCHODYNAMICS OF FAMILY LIFE. DIAGNOSIS AND TREATMENT OF FAMILY RELATIONSHIPS. BY NATHAN W. ACKERMAN, M.D., Associate Clinical Professor of Psychiatry, Columbia University. Pp. 379. New York: Basic Books, Inc., 1958. Price, $6.75.

To the many contributions in this area he has already published, Doctor Ackerman has now added this treatise which is certainly a pioneer and may prove a classic. Though longish, it includes such vast material as to deserve high marks for compression. The author states his theme as ". . . the outgrowth of an idea, a point of view concerning mental illness and health . . . a way of understanding health through the emotional 'give and take' of family relationships . . . a conceptual approach to emotional disturbance in the individual through analysis of the psychological content of his family experience."

Part I, Theoretical Aspects, outlines a critical revision of Freudian theory (let theoretical amateurs be wary here!) and applies the homeostasis concept to intra-familial psychological equilibrium. Part II, Clinical Aspects, discusses, with illuminating clinical examples, aims and techniques of family (as contrasted with individual) diagnosis, and Part III, Therapeutic Aspects, does the same for therapy. Parts II and III especially make rewarding reading. Part IV, Wider Perspectives, suggests lines of research for the future,

and considers trends of desirable social evolution.

The extensive bibliography is valuable. There is a complete and accurate index.

M.B.

Bibliography of International Congresses of Medical Sciences. Prepared by W. J. BISHOP under the auspices of the Council for International Organizations of Medical Sciences with the financial assistance of Unesco. Pp. 238. Springfield, Ill.: Charles C Thomas, 1958. Price, $5.50.

A LIST of international congresses alphabetically arranged by subject and group and with references on publications and transactions. R.K.

An International Nomenclature of Yaws Lesions. By C. J. HACKETT, in cooperation with an International Group of Experts on Yaws and participants at the International Conference on Yaws Control, Enugu, Nigeria, 1955. Pp. 103; 76 ills. Geneva: World Health Organization, 1957. Price, $4.00.

OVER the years any cooperative international efforts in the study and control of yaws have been handicapped by the confusion in the literature on the subject resulting from the faulty and incalculable terminology in use from country to country. The first major corrective step was the adoption of a classification of yaws lesions in 1952 by the First International Symposium on Yaws, in Bangkok. This volume, the product of a group of 18 persons with practical experience in yaws and from 16 different countries, restudies that classification, together with the commoner synonyms in current use. Its chief purpose is to illustrate by photographs the actual lesions to which the terms apply. That a picture is worth a thousand words is amply proved by the 76 excellent photographs that make up the bulk of the volume. R.K.

New and Nonofficial Drugs, 1958. A.M.A. Council on Drugs. Pp. 645. Philadelphia: J. B. Lippincott Company, 1958. Price, $3.35.

A ROUTINE word of advice to each senior medical student is to caution him not to learn his therapeutics from the detail man. Of equal moment is the injunction that he keep a copy of the current edition of New and Nonofficial Drugs on his desk: It is a basic necessity in the practice of medicine. This new volume, like its predecessors, continues to grow in size as well as importance. There have been added 48 monographs on new preparations as against 13 deletions. R.K.

Autonomic Imbalance and the Hypothalamus. By ERNST GELLHORN, M.D., PH.D., Professor of Neurophysiology, University of Minnesota. Pp. 300; 101 ills. Minneapolis: University of Minnesota Press, 1957. Price, $8.50.

IN this monograph, the author describes a series of experiments which deal with the excitability of the hypothalamus in the intact organism as measured through autonomic tests. The material is presented in two major sections, the first encompasses "Experimental Investigations," and the second a "Review of Results and Clinical Application." Among the topics considered are the physiological laws concerning autonomic imbalance; hypothalamic excitability, phasic autonomic reflexes, and tonic autonomic functions; the relation of hypothalamic excitation to neurogenic and hormonal discharges; and the action of drugs on the hypothalamic-cortical system. The central role of the hypothalamus in the physiology of emotions and behavior is well-delineated.

Neuropsychiatrists, psychologists, and physiologists will find much of interest and value in this volume. C.Z.

International Sanitary Regulations. Pp. 129; 3 ills. Geneva: World Health Organization, 1957. Price, $1.00.

THE purpose of the International Sanitary Regulations is to insure the greatest possible protection against six of the most epidemic diseases: yellow fever, cholera, plague, smallpox, typhus and relapsing fevers. The regulations were first adopted by the World Health Assembly in 1951 and have been three times amended. This new edition has been designed primarily to meet the practical needs of port and airport health administrators and others concerned with the application of the regulations. There is full coverage of modifications or reservations that apply in any particular country. R.K.

Atomic Energy in Medicine. By K. E. HALNAN. Pp. 157; 31 ills. New York: Philosophical Library, Inc., 1957. Price, $6.00.

THIS book was written to serve as an introduction to the use of radioisotopes in medical research, diagnosis, and therapy. The author deals clearly and authoritatively with atomic physics, the principles of use of radioactive isotopes, radiobiology, cancer and radiotherapy, and other clinical uses of these substances. There are also interesting discussions of the problems and hazards of radiation, and of the future developments which may be anticipated in this field. Medical students and others wishing to read a not overly technical treatise on the uses of atomic energy in medicine will find this volume suitable for their purpose. C.Z.

Our Nuclear Adventure: Its Possibilities and Perils. By D. G. ARNOTT. Pp. 170; 17 ills. New York: Philosophical Library, Inc., 1958. Price, $6.00.

THIS small book is written to inform the public at large of the perils of nuclear energy, and of

the constructive possibilities to which the same power source may be directed. The material is presented in 4 major sections: Part I, Basic Information; Part II, Co-Annihilation; Part III, Power Unlimited; and Part IV, Living with the Nucleus.

The author has succeeded in producing a clear readable exposition of what is a highly complex and highly important subject. In addition, he discusses in a provocative manner the philosophic and ethical questions which have arisen with the nuclear weapons. This book may be recommended to the general reader who desires a nontechnical introduction to atomic power and the problems that its availability have created.

C.Z.

Practical Use of the Office Laboratory and X-ray Including the Electrocardiograph. By Paul Williamson, M.D. Pp. 323; illustrated. St. Louis: C. V. Mosby Co., 1957. Price, $10.75.

This volume sets forth a number of commonly employed laboratory and Roentgen-ray procedures which can be performed by "a home-trained technician in any office with a minimum of basic equipment." In addition, the author offers his interpretation of the test results and findings of office electrocardiography and roentgenography.

General practitioners may find this somewhat oversimplified presentation of laboratory methods of value in an office practice.

C.Z.

Principles of Research in Biology and Medicine. By Dwight J. Ingle, B.S., M.S., Ph.D., Professor of Physiology, the Ben May Laboratory for Cancer Research, University of Chicago. Pp. 123. Philadelphia: J. B. Lippincott Co., 1958. Price, $4.75.

This small volume is an introduction to principles of research for students of biology and medicine. After an interesting opening chapter in which the general aims and methods of science are considered, the author deals successively with Limitations of Mind; Causality; Probability, Chance, and Randomization; Errors; Heteropoietic Factors; Principles of Testing; The Experiment; Interpretation of Results; Theory in Biology and Medicine; and Relationships Among Scientists.

Dr. Ingle, who has a long experience as an investigator, has succeeded in producing an instructive, and at times provocative, presentation of various fundamental considerations applicable to the general area of research in medicine and biology. This book may be read with interest and profit by all who are concerned with investigative medicine.

C.Z.

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